Ciro Esposito
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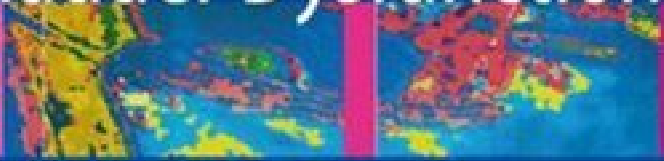
Editors

Pediatric Neurogenic Bladder Dysfunction



Diagnosis
Treatment
Long-Term Follow-up

DVD-VIDEO
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Ciro Esposito · Jean Michel Guys · David Gough · Antonio Savanelli (Eds.)

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Diagnosis, Treatment, Long-Term Follow-up

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With 137 Figures, 57 in Color and 50 Tables

Springer

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To our families who support us daily
with their love.

To our mentors:
Michel Carcassonne, Giovanni Esposito
and Gerard Monfort
who have shown us the way.

To our friend David,
teacher of pediatric urology.

And to the children we care for every day.

Ciro Esposito, Jean Michel Guys,
Antonio Savanelli

Foreword

It is a privilege to comment on this excellent volume, *Pediatric Neurogenic Bladder Dysfunction*, edited by C. Esposito, J.M. Guys, D. Gough, and A. Savanelli.

Knowledge in pediatric surgical science is increasing rapidly. With regard to the specific field of neurogenic bladder, this book covers the functional pathophysiology of the lower urinary tract, the pathologies responsible for the development of neurogenic bladder dysfunction (NBD), evaluation and classification of NBD, conservative treatment, surgical treatment, complications, and prognosis.

With the explosive development of modern surgical science, surgical practices have become increasingly more specialized, which has led to an increasing need for focus on specific issues. At the same time, specialized fields require multidisciplinary interactions: pediatric surgeons, pediatricians, radiologists, pediatric nephrologists, and others must cooperate as a team. This volume, therefore, is not only targeted to pediatric surgeons and pediatricians, but also to several other specialists.

For those practitioners who work as teachers, it should be remembered that research and teaching are not distinct practices but instead must be integrated within a research-oriented environment. Quality of research, teaching, and clinical practice is reciprocally rewarding. Obviously, this is not to say that every pediatrician or pediatric surgeon must be involved in all three types of activity; it is meant only as a call for continued communication between these three types of activities in the medical and surgical pediatric domain. We should all work to maintain a strong link between research, teaching, and health care.

This volume is an excellent example of how generation of new scientific knowledge, transmission of that knowledge, and application of newly developed principles, methods, and techniques into practice can find a good synthesis for the benefit of all concerned researchers and specialists.

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Preface

During the past decades the rapid advances in pediatric urology have reflected an era of fast growth in all fields of scientific knowledge, from pathophysiology to diagnosis, and from therapy to prevention.

To confirm the increasing interest in pediatric urology in the past 10 years, there have been many articles and books focusing on general or specific aspects of this field, useful both to undergraduate and postgraduate students; however, a publication concerned mainly with spina bifida and childrens' neurogenic bladder dysfunction in general still does not exist.

These pathologies present a broad range of problems in the children affected. We believe that this subject has become so important as to deserve a separate analysis in this book.

Our goal has been to unite the specialists in this field in order to collect the updated data on prevention, diagnosis, treatment, and follow-up of the disorders.

All the authors who participated in this project are considered leading world experts in the management of neurogenic bladder dysfunction, and we are extremely grateful to them for their contributions and for devoting their time to produce such outstanding reviews.

Another aim of our book is to offer a comprehensive, concise, and reader-friendly volume, directed to practitioners, urologists, pediatric surgeons, pediatricians, neurologists, nursing staff, and family associations interested in modern diagnostic and therapeutic techniques used in children with neurogenic bladder dysfunction.

The DVD included with the book, which reports the main diagnostic and therapeutic procedures carried out on children affected by neurogenic bladder dysfunction, represents an interesting and modern way of transmitting scientific knowledge.

The editing of this book would have been impossible without the precious cooperation and friendship of David Gough, who recently died.

The news of David's death was a shock to all in the pediatric urology community. We dedicate this book to his memory.

Ciro Esposito
Jean Michel Guys
Antonio Savanelli

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Embriology and Anatomy of the excretory Urinary Tract

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1.1
Embryology of the Urinary System

The urinary system appears in a very early phase of prenatal development, precisely when the embryo is about 2–6 mm long (Fig. 1). It develops in three distinct stages, during which evolutional and involutional processes contribute to form the definite urinary system, along with some structures of the genital system [25].

During the initial development phase two main buds grow: the first is the nephrogenic bud, which derives from the mesodermal pedicles placed between the dorsal and the lateral mesoderm; the second, the cloaca, represents the caudal extremity of the primitive bowel [25, 32, 33].

The nephrogenic bud, which undergoes a metameric segmentation dividing into nephrotomes placed between the somites and the lateral layers, develops into three buds: pronephros; mesonephros; and metanephros (Fig. 2).

The pronephros develops during the latter part of the third week of gestation. It is composed of five to nine buds which, after the twenty-first day, become hollow, forming the transversal tubules that constitute the primitive bud of the excretory urinary tract [25, 32, 33].

The more caudal tubules, which have in their medial layer ampullar introflexions, contain the arterial glomerules, and join at their distal extension to form the collecting duct of the pronephros, which eventually, at 28 days of gestation, enters the side of the cloaca [22].

In the next phase, at the end of the fourth week of gestation, we have the atrophy of the trasversal tubules and part of the collecting duct of the pronephros, which marks the beginning of the development of mesonephros or Wolff’s body [23, 25].

Towards the middle of the second month, the buds of Wolff’s body merge in a similar fashion, into a cord that gives rise to many little spheres which swell to form the transversal tubules of mesonephros; the latter flows into the remaining collecting duct of the mesonephros, called Wolff’s duct in the primitive urethra [32, 33].

Subsequently, the transversal tubules differentiate into secretory tubules and collecting tubules enlarged medially to form the ampullas; these form the arterial glomerules. In a subsequent phase, when the embryo is about 8 mm long, Wolf’s duct, which merges with the urogenital portion of the cloaca, gives rise to the ureteral bud, which grows dorsal to separate from Wolff’s duct and join in the dorsal portion of subsiding urogenital sinus [25, 31].

In a terminal phase (eighth week of gestation), when the embryo is about 25–30 mm long, the cranial portion of the mesonephros disappears, while the residual portion changes differently on the basis of the gender of the embryo [25].

In males, this upper portion gives rise to the epididymis head, the rete testis, and the superior paradidymis, whereas its lower portion undergoes atrophy, except for the part that forms the inferior epididymis [14, 23, 31].

In females, the entire mesonephros undergoes atrophy, except the part that forms the epoophoron and the paroophoron.

Wolff’s duct also undergoes different development according to gender: in females it undergoes atrophy, except for the portion that forms the epooforon duct and Malpighi Gartner’s duct, whereas in males it forms the tail and the body of the epididymis, the deferens, and the ejaculatory duct [14, 25].

At the same time as these modifications occur, the metanephros appears: it is composed of two buds that join to form the secretory part of the kidney, whereas the

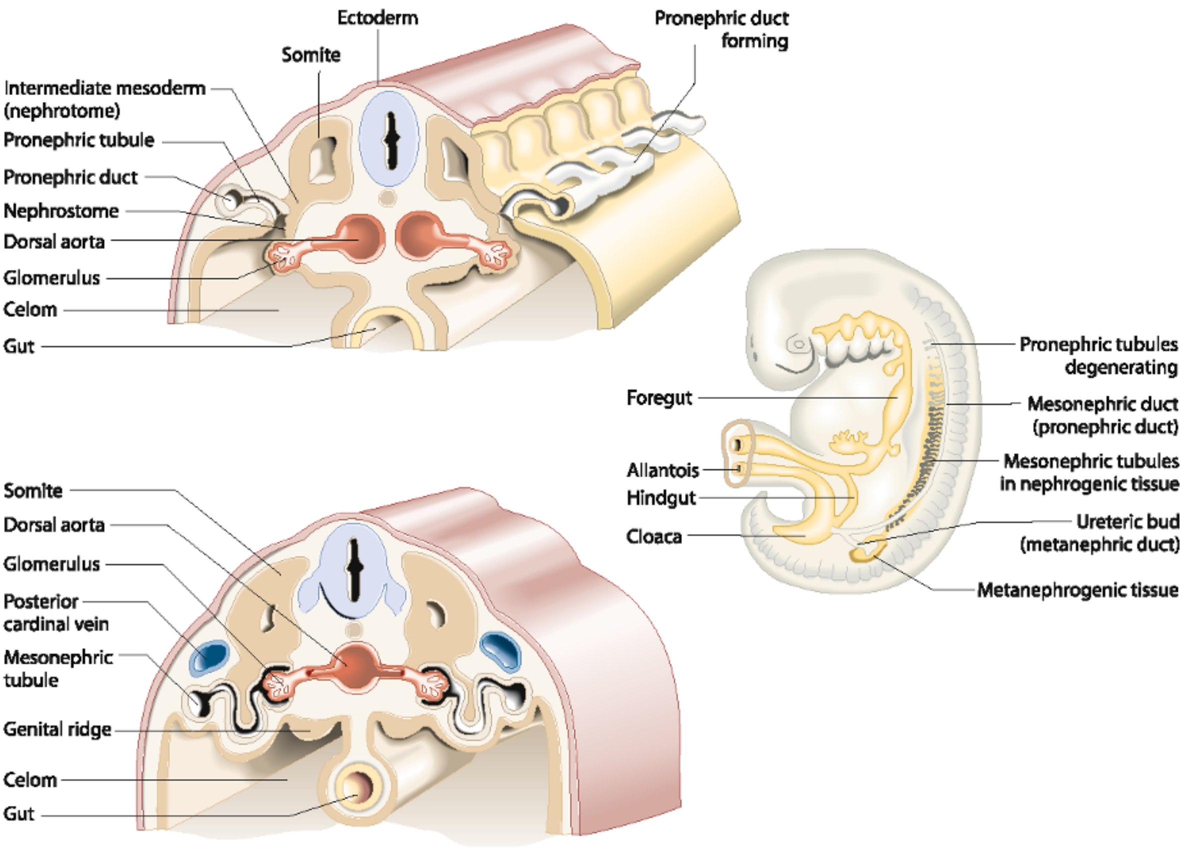


Fig. 1. Topography of pronephros, mesonephros, and metanephric primordium. (Modified from [25])

excretory part of this organ derives from the caudal part of Wolff's duct, which gives rise to the ureteral buds.

After its origin, the urethra dilates and grows both upwards and downwards, entering the metanephrogenic tissue and forming the primitive pelvis, the collectors of the first orders (which become the major renal calyces), the collectors of the second order (which become minor renal calyces, and the collector of the third order (the papillary ducts and collecting tubules) [25, 32, 33].

Once the metanephrogenic tissue has enveloped the primitive renal pelvis, it subdivides into tubules that form the basic unit of the kidney, after penetrating the glomerular artery. This is the so-called nephron, which extends from Bowman's capsula to the union segment that joins the collecting tubule [2, 14, 25].

In a subsequent phase, the pyramid renal lobes and the renal columns of Bertin extend to the periphery of the glomerules, form Ferrein's tubules and the central predominance of Bellini's tubules. At this stage, the kidney has achieved its definite form, with the typical medullar and cortical zones.

The cloaca is divided by the urogenital septum into an anterior portion, connected to the digestive system, and a posterior portion, connected to the urogenital sinus, and receives, posteriorly the outlets of Wolff's duct and the ureters.

The plane that goes to the outlet of Wolff's ducts divides the urogenital sinus into an upper zone, the urinary one, and a lower zone, the genital one [25, 33].

The urinary zone gives rise anteriorly to the bladder and the primitive urethra, which develops in males into the initial portion of the definitive urethra until the veromontanum, and in females into the entire urethra.

Posteriorly the urinary zone in males develops into the prostatic urethra and the membranous one, and in females into the vestibule of the vagina [14, 25].

1.2
Anatomy of the Bladder

The bladder is a hollow organ composed of three layers. The outermost layer is the serosa, which consists of an adventitial coat of connective tissue limited by a thin layer of mesothelial cells. The middle, muscular layer comprises three layers of smooth muscle tissue: an inner and outer longitudinal layer and a middle circular layer. The very specialized, innermost layer is the epithelium,

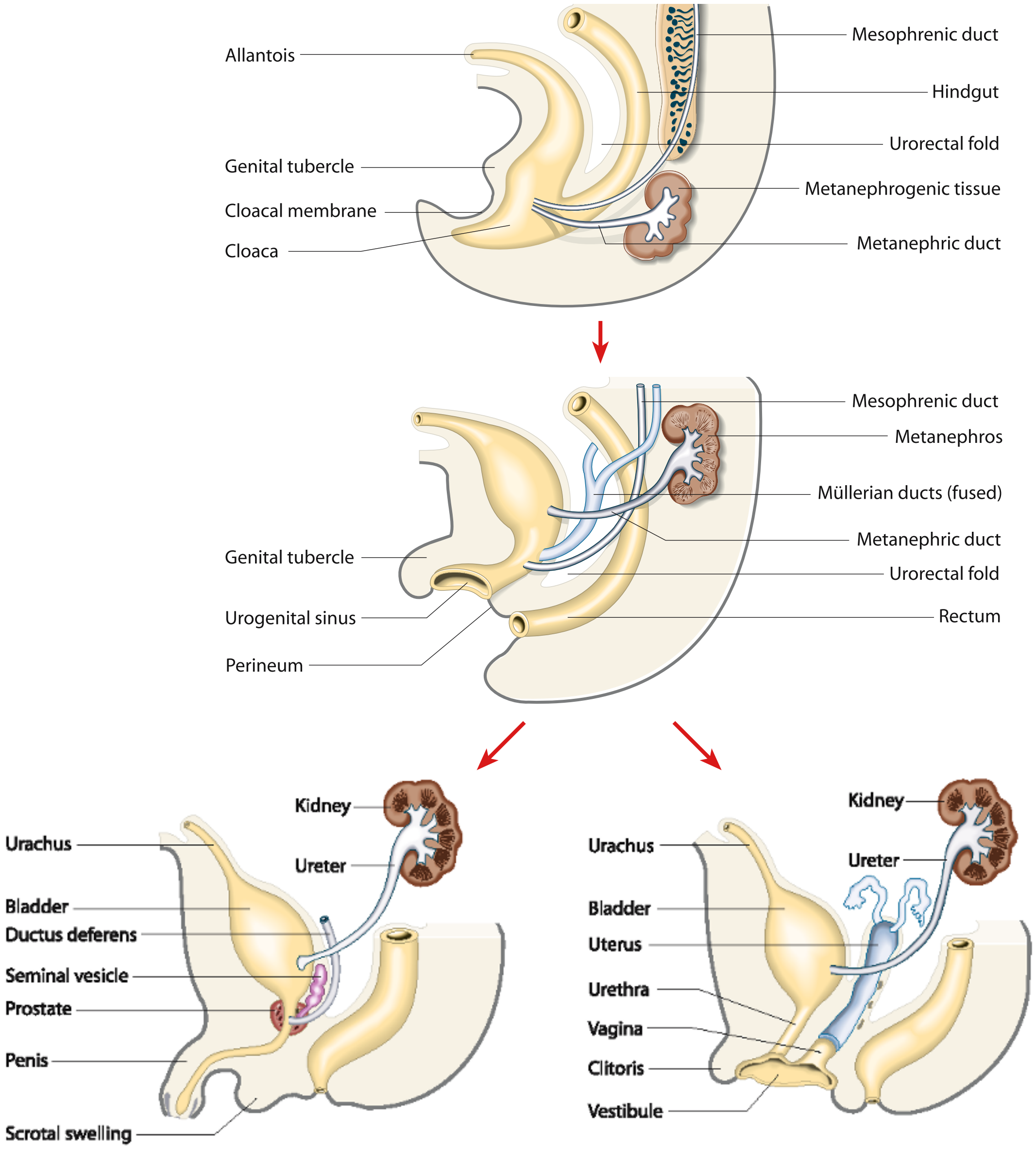


Fig. 2. Development of urinary bladder in male and female. (Modified from [25])

called the urothelium, which is separated from the muscle layer by the lamina propria [17].

1.2.1
Gross Anatomy of the Bladder

The spherical shape of the bladder permits a low surface-area-to-volume ratio that enables efficient accommodation of increasing volumes of urine and rapid and complete emptying when the muscle layers contract. Proposed mechanical models suggest that the pressure/volume relationship of the bladder is dependent on the variations of the spherical shape of the bladder [6, 22].

The serosa is formed by a sheet of wavy collagen bundles. Its structure allows the coordination of movement of the muscle layer, associated with the expansion and contraction of the bladder wall, while preventing overstretching of the bladder [24, 26].

The muscular layer comprises several layers of smooth muscle and extracellular matrix. The fundus or dome of the bladder is distensible, as well as capable of contraction, and thus is primarily responsible for the storage and expulsion of urine, whereas the relatively in-distensible and fixed base of the detrusor is important in the maintenance of continence and funneling of the bladder neck to permit efficient emptying of the bladder. The base of the bladder includes the triangularly shaped trigone, bounded by the bladder neck and the two ureteral orifices. The trigone has two muscle layers. The superficial muscle layer is formed by the muscular extensions of the two distal ureters, which becomes thickened along its edges and is referred to as Mercier's bar at its cephalad border, and Bell's muscles along its lateral and inferior edges. The deep trigonal layer is continuous with the detrusor in the fundus. Waldeyer's sheath refers to the craniolateral extensions of the base detrusor oriented longitudinally and helically to surround the distal end of each ureter. It is postulated that Waldeyer's sheath, along with the less clearly defined deep sheath derived from the ureteral muscularis itself, creates the dual sheath which prevents reflux of urine up the ureter by closure of its distal portion when the sheath contracts as an extension of the base of the detrusor [1, 9, 13]. The smooth muscle of the bladder neck (the junction of the bladder base and urethra) is structurally and functionally distinct from the muscle of the detrusor. In both sexes the muscle bundles are much smaller than those of the detrusor. In men these muscle bundles are oriented in a circular fashion around the bladder neck, which may aid in continence as well as prevent retrograde ejaculation. Distally, the fibers merge with the capsule of the prostate. In women these muscle bundles extend obliquely and longitudinally along the urethra so that there is no true internal sphincter [1].

The smooth muscle is loosely arranged in bundles (fascicles). Sheaths of collagen fibrils surround the individual muscle cells and collagen sheets surround the muscle fascicles. Elastin fibers are found primarily on the surface of the muscle fascicles. This arrangement allows each fascicle to move independently as a unit of contraction, while the perifascicular collagen sheets permit the independent motion of the muscle bundles and prevent over stretching. The deep muscular layer also contains flat tape-like bundles of parallel collagen fibers which are tightly coiled in the contracted state and straightened in the relaxed state, allowing it to withstand mechanical force in any direction [24].

Bladder wall thickness has been shown to decrease with bladder distension [35] . In animal studies the relative rate of lamina propria thinning with bladder distension is much greater than that of muscular thinning, suggesting the lamina propria is responsible for most of the capacitance of the bladder [4]. This is supported by theoretical models that show that hydrodynamic stiffness varies linearly with detrusor pressure, and that dynamic stiffness varies simultaneously with elastic and viscous components (the primary components of the lamina propria) of the bladder wall [36, 37].

A classic explanation for the relationship of bladder wall tension was proposed by Chancellor et al. [3] using Laplace's law of wall stress (wall stress=$PR_1/2h$), where P is pressure, R_1 is inner radius, and h is wall thickness; i.e., pressure within a balloon is equally transmitted to all parts, and tension in the wall varies with the radius in that portion [31].

1.2.2
Microscopic Anatomy of the Bladder

The detrusor muscle cells are very similar to other visceral smooth muscle cells. They are spindle shaped and vary in length and diameter (150–300 and 6–8 µm, respectively). When relaxed, they have a smooth surface and are polygonal in cross section. When contracted, they become scalloped in appearance with an irregular surface. A single, prominent and central nucleus is present with many mitochondria throughout the cytoplasm. The sacroplasmic reticulum is closely associated with flask-shaped invaginations of the cell membrane called caveoli. Within the cell, three types of filaments have been identified: thick (15-nm diameter, myosin); thin (6- to 8-nm diameter, actin); and intermediate (10-nm diameter, desmin or vimentin). The junctions between cells are primarily regions of close approach, where an intercellular separation of 10–20 nm exists. True gap junctions are not present. It is suggested that the regions of close approach may be the morphological feature that allows electronic coupling between cells [1, 13].

1.2.3
Vasculature of the Bladder

Animal studies have provided insights into the unique specializations of the bladder vasculature, which accommodates the broad range in bladder volume and wall tension associated with filling and emptying. The bladder is supplied by a rich vascular supply that runs in the serosal layer and the lamina propria . The right and left vesicular arteries extend along the lateral surface of the bladder from the base to the apex just deep to the serosal surface. Dorsal and ventral branches then supply the respective bladder walls. The branches of the arteries running deep into the muscle are coiled into "whirls and folds" providing excess vasculature to accommodate bladder filling. Sites of arterial anastomosis along the lateral edges of the base of the bladder enhance collateral circulation. The arteries are accompanied by veins with many valves. It is proposed that these multiple valves assist in maintaining a unidirectional flow of blood during bladder distension [18]. The design of the vasculature appears to be effective in its goal. An animal model has demonstrated that normal filling of the bladder does not alter bladder blood flow, and voiding results in a transient decrease of approximately 40% of resting blood flow. It has also been shown that the principal determinant of blood flow in the bladder is the intralumenal pressure of the organ [15]. The vasculature running within the lamina propria is a rich capillary plexus that runs within grooves on the underside of the epithelium that are arranged in a fine mesh-like pattern. The separation between the capillaries and the epithelium (0.3 μm) suggests that this may play a role in the transport of solutes across the bladder epithelium [21].

1.2.4
Innervation of the Bladder

A study of up to four mammalian species has demonstrated the presence of dual autonomic innervation of the bladder [8, 9]. Cholinergic muscular nerves arise as branches of intermuscular nerve bundles. These nerves follow a wavy course in the connective tissue separating the muscle bundles, and become smaller as they subdivide down into individual axons. They accompany interstitial blood vessels as neurovascular bundles. The terminal ramifications of these nerve fibers form an extremely intricate nucleated plexiform network of variscosities between and around individual muscle fibers (Fig. 3). The variscosities contain vesicles (usually agranular), microtubules, neurofilaments, a small amount of endoplasmic reticulum, and mitochondria. The terminal variscosities usually end 30–50 nm from the adjacent muscle cell as the neuromuscular or neuroeffector junction [8, 12]. Adrenergic muscular nerves are derived partly from nerve bundles and large nerve trunks composed of cholinergic and adrenergic nerve fibers. They give rise to vascular branches that run in the connective tissue alongside and within the muscle bundles. Whereas cholinergic muscular nerves are equally distributed throughout the detrusor dome and base, the adrenergic nerves are more abundant in the base than in the dome of the bladder [8]. A study of the mammalian bladder base has demonstrated axoaxonal synapses between contiguous adrenergic and cholinergic postganglionic neurons implicating that the activity of the smooth muscle may be in part regulated by interaxonal neurotransmission at the effector (muscle) cell level [9]. In the lamina propria, two freely connected groups of nerves have been identified: a deep one and a superficial one. In the deep layer, rich cholinergic and adrenergic perivascular networks are present throughout the bladder; however, the complexity is more prominent at the bladder base corresponding to the increased complexity of the accompanying vasculature. In the superficial layer, cholinergic and adrenergic nerves follow a tortuous course along arterioles and venules, and progressively increase in number at the bladder base where they are interwoven into a complex network [8]. The nerve supply of the epithelium consists of a few, widely spaced fibers at the bladder dome and a rich branching of fibers in the bladder base. Both cholinergic and adrenergic fibers appear to run perpendicular to the epithelium and branch into a Y- or T-shape. Adrenergic fibers are fine and end abruptly in the basal third of the epithelium, whereas cholinergic fibers have a slightly clubbed termination and arborize as a rich network between the basal epithelial cells through more than one-half the thickness of the epithelium [8, 9].

1.3
Anatomy of the Urethra and Paraurethral Tissues

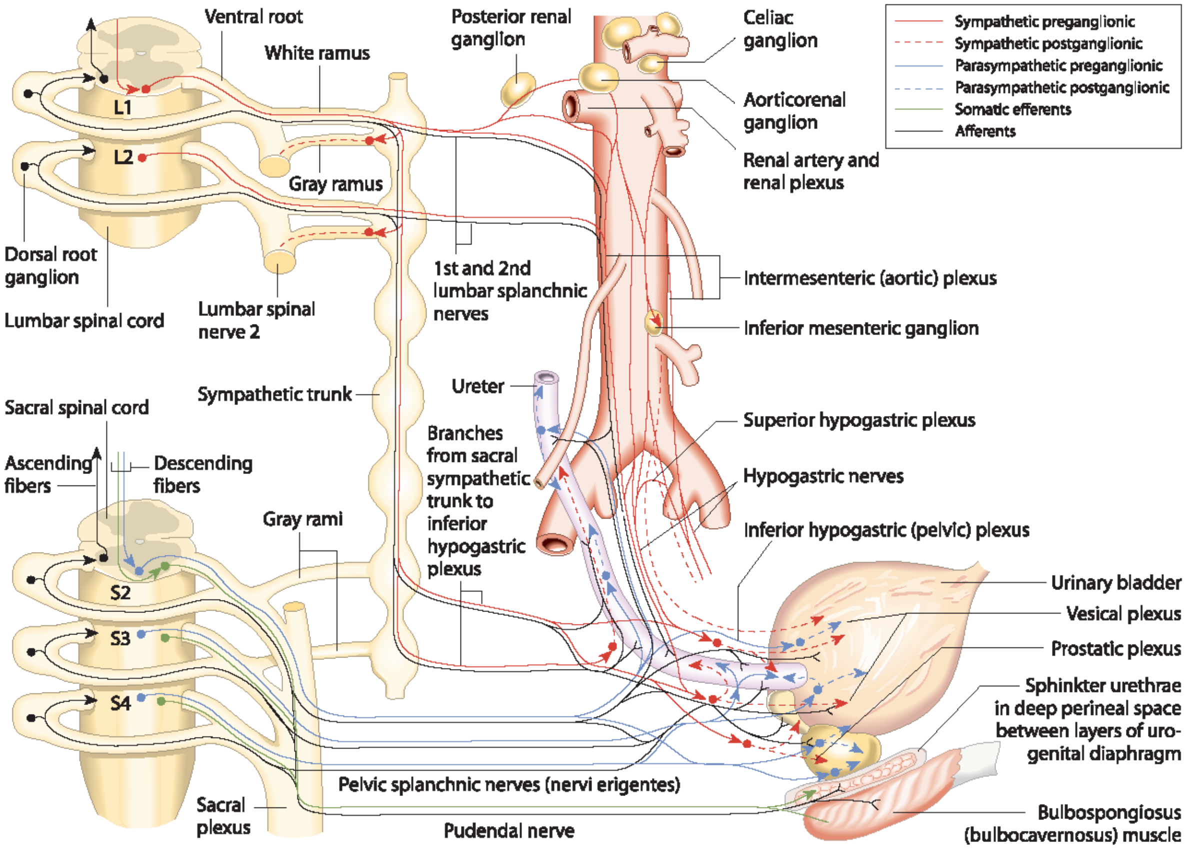
1.3.1
Gross Anatomy of the Urethra and Paraurethral Tissues

The male urethra has a length of 18–20 cm and is divided into three parts:

1. The prostatic urethra is the most proximal portion and is marked by the verumontanum in the posterior midline, and openings of the paired ejaculatory ducts and multiple prostatic ducts
2. The membranous urethra extends for less than 2 cm from the inferior margin of the prostate gland to the bulb of the corpus spongiosum
3. The penile urethra extends for approximately 15 cm through the corpus spongiosum of the penis (Fig. 4).

The female urethra is 2.5–3 cm in length and its mucosa is collapsed into longitudinal folds (Fig. 5) Above the urogenital diaphragm the neonatal urethra is crescent shaped because of the prominence of the crista urethralis. In adults this is less prominent and the urethral lumen is slit-like. Below the urogenital diaphragm the urethral lumen is star-shaped in all age groups because of the deep infoldings of the mucosa. A thick, vascular lamina propria lies underneath the mucosa [19, 20]. Paraurethral glandular ducts penetrate dorsolaterally [11, 19].

The striated urethral sphincter is described as being a signet-ring or horseshoe shape extending from the bladder neck with a roughly circular orientation of its fibers, which are deficient dorsally. The sphincter is bulkier and more well defined in the male and extends from the bladder to the urogenital diaphragm with some fibers of the sphincter merging into both these structures [9, 19, 28]. The muscle is associated with the prostate, and these two structures are surrounded by a common fascial sheath, such that they form a single unit [28]. In the female the striated sphincter extends the whole length of the urethra and is thickest in the middle third. Caudally it meets fibers of the urogenital diaphragm. Its fibers


Ventral root
White ramus
Posterior renal ganglion
Celiac ganglion
Aorticorenal ganglion
Renal artery and renal plexus
Sympathetic preganglionic
Sympathetic postganglionic
Parasympathetic preganglionic
Parasympathetic postganglionic
Somatic efferents
Afferents
L1
L2
Gray ramus
Dorsal root ganglion
Lumbar spinal cord
Lumbar spinal nerve 2
1st and 2nd lumbar splanchnic nerves
Intermesenteric (aortic) plexus
Inferior mesenteric ganglion
Sympathetic trunk
Ureter
Sacral spinal cord
Superior hypogastric plexus
Ascending fibers
Descending fibers
Branches from sacral sympathetic trunk to inferior hypogastric plexus
Hypogastric nerves
Gray rami
Inferior hypogastric (pelvic) plexus
S2
S3
S4
Urinary bladder
Vesical plexus
Prostatic plexus
Sphinkter urethrae in deep perineal space between layers of urogenital diaphragm
Pelvic splanchnic nerves (nervi erigentes)
Sacral plexus
Pudendal nerve
Bulbospongiosus (bulbocavernosus) muscle

thin out dorsally and appear to insert into a dorsal septum or raphe. Most sphincter fibers run circularly; however, some run longitudinally and insert into the bladder wall, endopelvic fascia, and vaginal wall [27]. The striated urethral sphincter has been shown to play a critical role in urethral closure pressure and maintenance of continence [5, 34].

The smooth muscle of the urethra is a continuation of the smooth muscle layers of the bladder. The superficial smooth muscle of the trigone extends inferiorly to the urogenital diaphragm and is continuous with the inner longitudinal smooth muscle layer of the urethra. The extension of the longitudinally directed outer smooth muscle layer of the bladder extends caudally to blend with the outer longitudinal layer of the urethra [19].

The urethra and bladder are supported by, and closely invested in, the pelvic floor structures. This includes the endopelvic fascia, the levator ani, and the perineal membrane [30]. The pubovesical ligaments extend from the detrusor muscle and adventitia, and insert into the pubic bone and arcus tendineus fasciae pelvis. The pubourethral ligaments extend from the vagina and periurethral tissues to the pelvic diaphragm and fascia, providing further urethral support [7].

1.3.2

Microscopic Anatomy of the Urethra and Paraurethral Tissues

The prostatic urethra is lined by the same transitional epithelium as the bladder, and a pseudostratified columnar epithelium lines the remainder of the urethra, with the exception of the most distal portion, which is lined by stratified squamous epithelium, the fossa navicularis [11]. The mucosa in the proximal portion of the female urethra is transitional and the distal urethra is covered by a non-keratinizing squamous epithelium. The cephalad extent of the squamous epithelium extends more proximally in older women [19, 20]. The ducts of the paraurethral glands are lined by cuboidal or pseudostratified columnar epithelium [19].

X-ray diffraction studies of the urethra have demonstrated that the predominant direction of urethral collagen fibers is longitudinal in the inner region and circular in the outer region [16].

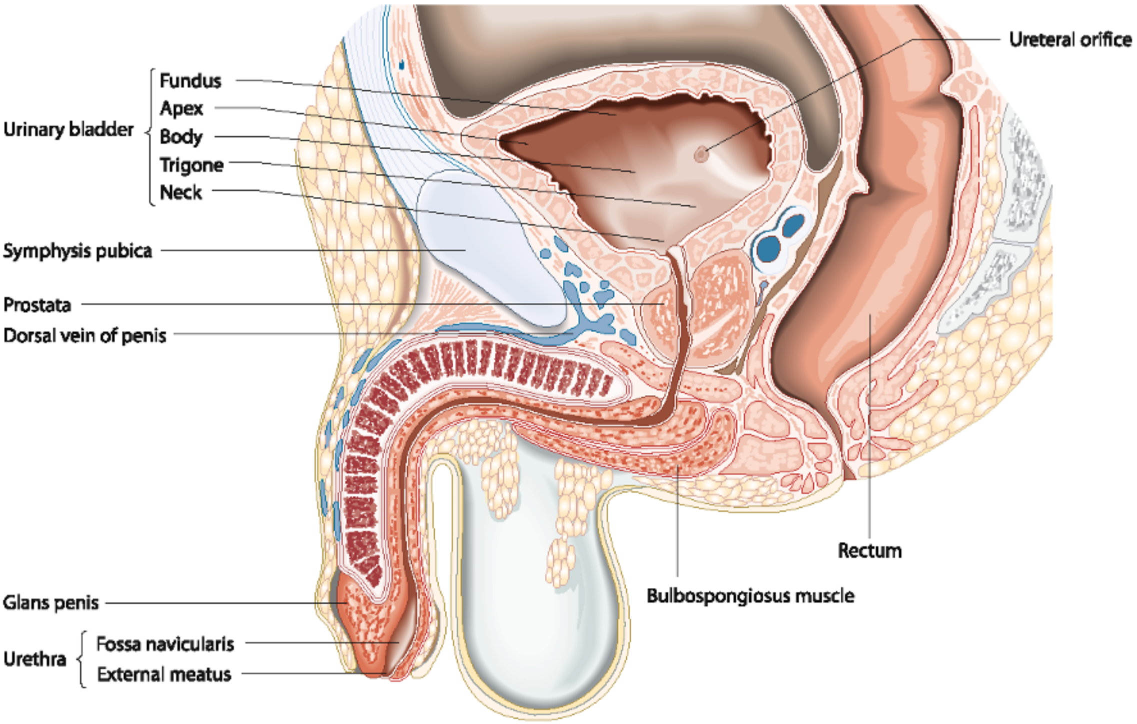


Fig. 4. Sagittal section of the male bladder and urethra. (Modified from [25])

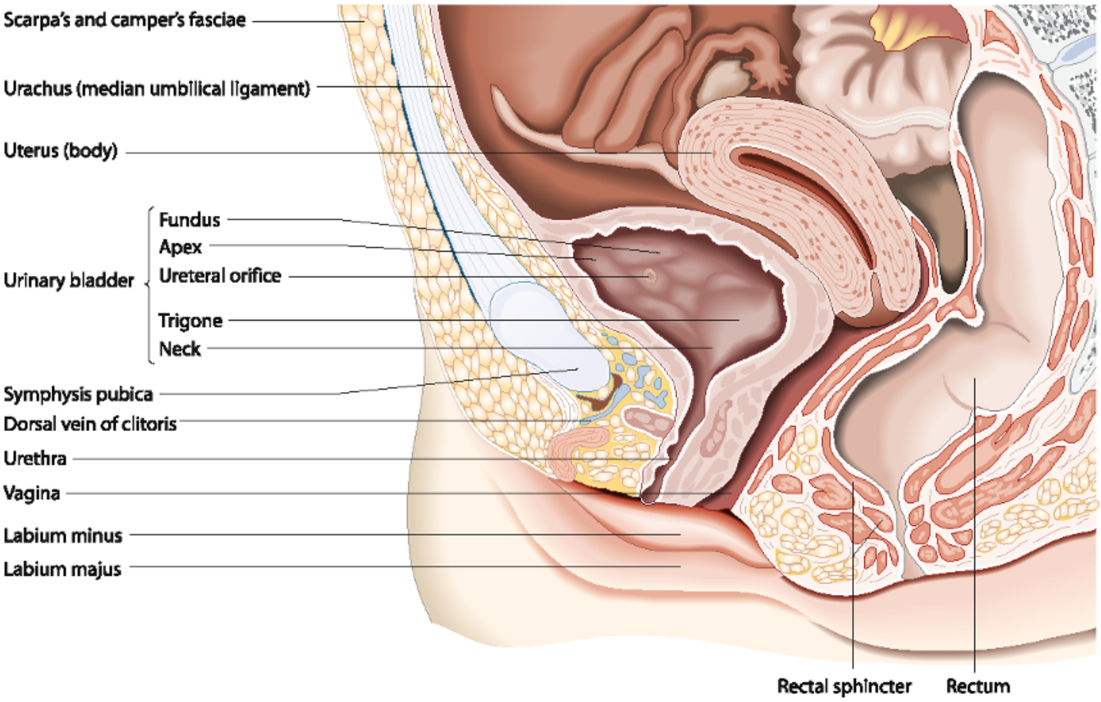


Fig. 5. Female urinary bladder and urethra. (Modified from [25])

1.3.3
Vasculature of the Urethra

Three venous systems are noted in the submucosa of the urethra: (a) a longitudinally oriented group of veins lying just underneath the epithelium, which are important in maintaining urethral coaptation; (b) a richly developed venous plexus in the proximal urethra formed by many arteriovenous anastomoses, which dilates and contributes to urethral pressure; and (c) a distal plexus just above the external urinary meatus. The arterial supply comes from the inferior vesical arteries. Two small branches penetrate the muscle of the bladder neck dorsolaterally and then divide into a muscular and submucosal branch [19]. Several studies have demonstrated how the vasculature of the urethral submucosa plays an important role in the maintenance of resting urethral closure pressure [10, 29].

1.3.4
Innervation of the Urethra

The urethral submucosa in both males and females contains a plexus of acetylcholinesterase-positive nerve fibers much like those of the bladder. Single nerve axons are noted in close approximation to the basal epithelium; many appear varicose and contain axonal vesicles (either clear/agranular or granular). This plexus is believed to have a sensory function [13].

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Physiology of the Lower Urinary Tract

2

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2.1
Introduction

The function of the bladder is to store urine at low pressure and empty efficiently at a socially acceptable time. This complex process involves integration of activity from the brain, brainstem, spinal cord, detrusor muscle, and external urethral sphincter (EUS). The unique anatomic, biomechanical, and physiological properties, which are critical for the normal function of the lower urinary tract, are highlighted herein. The current understanding of the neural control of the lower urinary tract, including the role of the peripheral and central nervous systems, sacral reflexes, and the development of neural control of bladder function, are explored. The pharmacological basis of urine storage and voiding are reviewed. The knowledge of the anatomy is fundamental to understand the physiology of the bladder; however, the anatomy of the bladder and urethra are discussed in another chapter.

2.2
Physiology of the Bladder

2.2.1
Contraction of Smooth Muscle

Smooth muscle cell contraction and tone is dependent on the interaction of the intracellular filaments actin (which attaches to the cell membrane at sites called dense bodies) and myosin (which is free within the cytoplasm). The contraction of smooth muscle is regulated by the intracellular concentration of free Ca^{2+} [15].

The resting membrane potential of human detrusor smooth muscle cells has been estimated to be approximately −40 mV by a whole-cell patch clamp technique. Spontaneous action potentials do occur. The depolarizing phase of the action potential occurs as a result of inward passage of Ca^{2+} ions. Repolarization occurs in response to an outward flow of K^+ current that is partially Ca^{2+} dependent [73, 76].

In the sliding filament model the heads of myosin molecules alternate between a high- and low-affinity binding state with the thin actin filaments. This binding is driven by ATP hydrolysis and causes a change in the angle of the myosin heads that results in sliding of the thick myosin filament past the thin filament when the myosin light chain is phosphorylated. With stimulation of the smooth muscle cells a rise in intracellular Ca^{2+} results in myosin light chain kinase (MLCK) phosphorylation by cAMP-dependent protein kinase. The activated MLCK phosphorylates the myosin light chain and contraction of the muscle cells occurs. Relaxation is regulated by the dephosphorylation by myosin light chain phosphatase. The free Ca^{2+} binds to the protein calmodulin and the Ca^{2+}-calmodulin complex binds to the dephosphorylated myosin light chain kinase. The biochemical mechanism of the formation of a “latch” state in which force is maintained and the utilization of ATP is very low and cycling of cross-bridges is slow or absent is postulated to occur when an attached cross-bridge is dephosphorylated. The exact mechanism has not yet been elucidated [15, 42].

The kidneys yield urine with a high concentration of solutes and toxins that are stored in the bladder prior to excretion. The bladder urothelium is highly impermeable. This property acts to prevent the passive absorption of these molecules [25, 34, 59]. The structure of the urothelium plays a critical role in this function. The urothelium is three to seven cell layers thick and exhibits a pattern of increasingly differentiated cells from its base to its lumenal surface. The cells of the basal layer are relatively small and undifferentiated, cells of the intermediate layer are slightly larger, and the umbrella cells at the surface are large, flattened, highly differentiated cells which are frequently binucleate. Turnover of the urothelium is extremely slow (0.01–0.1%) [45, 49]. The shape of the apical cells is squamous in the distended bladder but becomes cuboidal when the bladder contracts [72]. An important component in the urothelial impermeability is the glycocalyx, a layer superficial to the umbrella cell layer that is composed of highly charged proteoglycans and glycoproteins that are ionically linked together. The proteoglycans, also known as glycosaminoglycans (GAGS), are negatively charged and the high density of charge at the surface of the urothelium leads to a strong ordering of water molecules at the bladder surface, thus contributing to the impermeability of the bladder wall [49]. The GAG layer has been implicated in the prevention of bacterial adherence [43].

The umbrella cell layer is noted to have an asymmetric unit membrane composed of specialized integral membrane proteins called uroplakins, believed to have a role in the plasma-urine barrier. Four uroplakins have been identified (Ia, Ib, II, and III). Most of the hydrophilic domains of these proteins are extracellular and exist in the bladder lumen where they interact closely with one another [91, 108]. Freeze etching of the lumenal surface reveals hexagonally patterned, rigid plaques with flexible interplaque (“hinge”) regions. Long cytoplasmic filaments seem to be attached to the hexagonal plaques via short cross-bridging filaments. It is suggested that the hinge regions allow the membrane to fold when the bladder is contracted [90]. Another proposed mechanism for folding of the lumenal membrane is the formation of unique disc-shaped vesicles when two adjacent cell membranes fuse with a bladder contraction [60, 61, 85].

The transepithelial resistance of the urothelium lies primarily within the apical cell layer due to radial cell-to-cell coupling. This resistance is maintained by tight junctions and the extrusion of Na^{2+} by a basolateral Na^{2+}-K^{+}-ATPase pump [63, 84]. Transepithelial movement of solutes may occur via one of two parallel pathways: (a) transcellular by transportation across the apical membrane of the epithelium; or (b) paracellular across the tight junctions with diffusion through the lateral intercellular space and basement membrane [62].

2.3 Neural Control of the Lower Urinary Tract

The process of micturition is coordinated by various levels of inhibition and facilitation throughout the central and peripheral nervous system that results in low-pressure storage of urine and efficient bladder emptying with an organized bladder contraction and sphincter relaxation. Afferent and efferent signals pass from the lower urinary tract to the spinal cord via peripheral pathways. Descending input from higher spinal cord and cephalic levels modulates these signals.

2.3.1 Peripheral Nervous System

In both sexes the detrusor, bladder neck, and urethra are innervated by branches of the pelvic plexus. This plexus is formed by ramifications of the trunks of both the pelvic (parasympathetic) and hypogastric (sympathetic) nerves, and incorporates ganglia that serve as relay stations [31].

The pelvic nerve is formed by three or four efferent trunks which originate from the parasympathetic nuclei located in the intermediolateral column of the gray matter of S2–S4 segments of the sacral spinal cord [13, 14, 26, 31, 82]. The relative contribution of each sacral level is variable. The detrusor and urethral supply is primarily S3; however, occasionally S2 or S4 may be predominant [13, 14]. These preganglionic axons leave the spinal cord and travel in the pelvic nerves to ganglia located in the pelvic plexus, on the surface of the bladder (vesical ganglia), or within the walls of the bladder and urethra (intramural ganglia) [64]. Postganglionic axons leave the pelvic, vesical, or intramural ganglia to innervate the smooth muscle of the lower urinary tract.

Efferent sympathetic innervation originates from the sympathetic nuclei located in the intermediolateral column of the gray matter to T10 to L2 segments of the spinal cord. These preganglionic neurons leave the spinal cord via the splanchnic nerves and either travel to the inferior mesenteric ganglion or pass caudally in the paravertebral chains to the level of the lumbosacral sympathetic chain ganglia. These preganglionic neurons may or may not synapse in the ganglia, so that both pre- and post-ganglionic sympathetic axons travel together in the hypogastic nerve to the pelvic plexus or the lower urinary tract [13, 64].

Afferent pathways from the bladder and urethra travel to the pelvic plexus and reach the dorsal root ganglia of the spinal cord via the pelvic and hypogastric nerves. These pathways then reach higher centers via the spinothalamic tracts [12, 31, 79].

Efferent innervation of the external urethral sphincter originates in Onuf’s nucleus located in the ventral

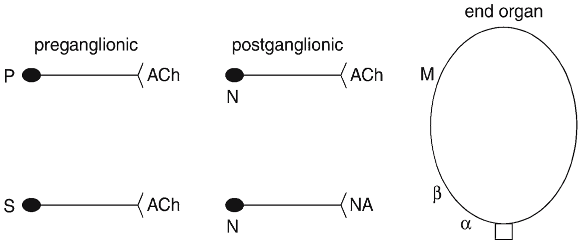

Fig. 1. Primary neurotransmitters and receptors in the lower urinary tract. *P* parasympathetic, *S* sympathetic, *Ach* acetylcholine, *N* nicotinic receptor, *M* muscarinic, *NA* noradrenaline, *β* beta receptor, *α* alpha receptor

horn of the sacral spinal cord primarily at the S3 level. The somatomotor nerves are relayed directly to the sphincter by the pudendal nerves that travels in Alcock's canal [52, 71, 93, 97, 98]. There is evidence to suggest that the pelvic nerve provides some somatic fibers to the external urethral sphincter [74].

Interactions between the peripheral pathways (parasympathetic, sympathetic, and somatic) can occur at the level of the spinal cord, within the autonomic ganglia, or at the neuromuscular junction. Investigations in several mammalian species have suggested the presence of neuromodulation of adrenergic and cholinergic nerves by postganglionic adrenergic and cholinergic nerves and short neurons (or interneurons) which result in either autoregulation of a pathway or regulation of the alternate pathway (e.g., inhibition of parasympathetic action by sympathetic neurons at the neuromuscular junction) [32, 33, 68, 69].

2.3.2
Central Nervous System

The central nervous system modulates the function of the lower urinary tract with both inhibitory and facilatory influences. The cerebral sites of modulation include the anterior cingulated gyrus, amygdala, paracentral lobule, pre-optic nucleus, pontine reticular formation, subcallosal cingulate gyrus, septal area, and the superior frontal gyrus [86, 99].

In the human and other species, the most significant area for detrusor control is the superior frontal gyrus [99]. There is convincing evidence to suggest that this control is localized primarily in the right side of the brain [35, 58]. The pontine micturition area is the area that coordinates and integrates the bladder and sphincter function. It plays an important role in bladder storage and release. Its importance has been demonstrated in many species including the human, rat, and cat. Lesions above this level lead to coordinated incontinence and lesions below this level result in incoordination and detrusor sphincter dyssynergia [11, 67, 82, 99]. For an excellent review of the role of the central nervous system in lower urinary tract physiology see de Groat [21].

2.3.3
Lower Urinary Tract Reflexes

The complex coordination of sensory and motor pathways to allow storage of urine at low pressure and efficient bladder emptying at a socially acceptable time requires connections between the sensimotor cortex and the pudendal nucleus that control voluntary sphincter activity. Voluntary control of voiding is integrated by complex interactions among cortical areas (frontal cortex), subcortical areas (thalamus, hypothalamus, basal ganglia, and limbic system) and brain stem (mesencephalic-pontine-medullary reticular formation) [8]. Historically, it was believed that the voiding reflex was mediated at the spinal level. This was discredited by the recognition that a majority of patients with supraspinal cord lesions do not have normal voiding. (For an excellent review of the development of knowledge about micturition reflexes see [31].)

2.3.3.1
Bladder Sensation

Micturition is a reflex initiated by myelinated A-fiber receptors in the mucosa and submucosa of the bladder [23]. These free nerve endings act as mechanoreceptors, activated by bladder stretch with low-pressure thresholds ($\leq$10 mmHg). They may also function as chemoreceptors as they are activated by intravesical instillation of noxious agents [88], although unmyelinated C-fibers are thought to be the predominant pathway for afferent noxious stimuli [87]. The normal micturition reflex elicited by A-fiber afferents is initially lost in cats with a suprasacral transection of the spinal cord. A spinally mediated bladder micturition reflex gradually returns, but it is elicited by C-fibers [23].

2.3.3.2
Reflexes Involved in Bladder Storage

Bladder distension results in afferent pelvic nerve discharge. After synapsing in the pudendal nucleus efferent pudendal nerve impulses result in a detrusor contraction of EUS [9, 36, 104]. At the same time afferent sympathetic discharges traverse the hypogastric nerve. After they synapse in sympathetic nuclei efferent firing causes (a) inhibition of transmission at postganglionic parasympathetic neuron, which inhibits a detrusor contraction, and (b) increases tone at the bladder neck. The net effect is that urethral pressure remains greater than detrusor pressure, facilitating urine storage [8, 10, 24, 28, 57].

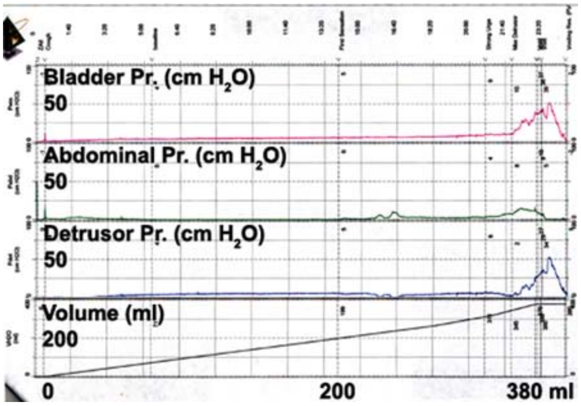

Fig. 2. A normal urodynamic study demonstrating bladder filling at low pressures indicating normal bladder compliance and a normal bladder contraction with voiding. *Pr* pressure, *cm* H_2O centrimetres of water pressure, *mL* millilitres

2.3.3.3
Reflexes Involved in Voiding

Afferent pelvic nerve discharges ascend the spinal cord and synapse in the pontine micturition center. Descending efferent pathways cause (a) inhibition of pudendal firing which relaxes the EUS, (b) inhibition of sympathetic firing, which opens the bladder neck and permits postganglionic parasympathetic transmission, and (c) facilitation of pelvic parasympathetics which causes the detrusor to contract. This results in relaxation of the EUS causing a decrease in urethral pressure followed almost immediately by a detrusor contraction leading to voiding [8, 9, 36, 92, 94]. Voluntary interruption of urinary stream is mediated by descending cortical spinal pathways that emanate from motor cortex which synapse in the pudendal nucleus. This results in contraction of the EUS, increasing urethral pressure above detrusor pressure and interruption of the stream [8].

2.3.4
Development of Neural Control

In the past, it was believed that voiding in the infant was automatic and uninhibited, a reflex initiated by a specific bladder volume confined to the level of the sacral spinal cord without cortical input. The development of bladder control was thought to be related to maturation of neural pathways [65, 77, 80]. Studies have demonstrated the plasticity and maturation of the neural pathways responsible for micturition [5, 66, 98]. The concept of uninhibited infant voiding that is unmodified by higher, cortical input has been challenged by the demonstration that infants void while awake or during arousal from sleep and never during quiet sleep, suggesting there is cortical arousal in response to bladder distension [106]. It is suggested that the pathways between the peripheral and central nervous systems are well formed at birth and the development of voluntary control represents a modification of pre-existing reflexes [106]. This theory is supported by the demonstration of an increased proportion of fully awake voiding in normal neonates compared with premature babies [89]. Further support of this concept is the stepwise decrease in the percentage of interrupted voiding episodes. Discoordination between the sphincter and detrusor is thought to lead to interrupted voiding, which is demonstrated in 58% of premature infants [89], 33% in full term infants at 3 months of age, but rarely noted after 2 years of age [50]. The demonstration that voiding pressures in infants are not excessive [50, 83, 103] and that the bladder wall in normal infants is not thickened [51, 105] lends further credence to the theory that higher cortical input plays an important role in the voiding reflex of neonates.

2.4
Pharmacology of the Lower Urinary Tract

2.4.1
Cholinergic Mechanisms

It is well established that preganglionic parasympathetic nerves release acetylcholine (Ach) [99] to nicotinic receptors of postganglionic nerves. The parasympathetic postganglionic nerves then release Ach to muscarinic receptors in the detrusor wall. The muscarinic receptor subtypes, M2 and M3, mediate the contraction of smooth muscle in the detrusor. The ratio of M2:M3 receptors in the detrusor is 3:1; however, direct contraction of smooth muscle is primarily mediated via the M3 receptor subtype [100]. The action of M2 receptors is mediated by adenylate cyclase and the action of M3 receptors is mediated by phospholipase C. Activation of the muscarinic acetylcholine receptor, M3, results in coupling to the G protein Gq, mobilizing IP3 and DAG, and, consequently, elevating intracellular Ca2+ levels [29, 44].

Studies in many species have demonstrated the uniform distribution of ACh containing nerves in the detrusor [1, 7, 16, 30, 38, 56, 102], bladder neck, and urethra [1, 30, 38, 39, 102].

2.4.2
Adrenergic Mechanisms

Preganglionic nerves release ACh to nicotinic receptors of postganglionic nerves. The postganglionic nerves then release noradrenaline to the adrenergic receptors of the lower urinary tract. The majority of bladder neck adrenergic receptors are the alpha1 (α1) subtype, whereas those of the bladder dome are primarily beta2 (β2) receptors [7, 68, 99].

Studies in many mammalian species have demonstrated sparse adrenergic nerve endings in the detrusor wall [6, 30, 38, 102] and dense innervation in the bladder neck and proximal urethra [1, 30, 37, 39, 56, 102]. Free ends of adrenergic nerves have been noted to approximate the EUS [37].

2.4.3
Nonadrenergic, Noncholinergic Mechanisms

The is an ever increasing large volume of evidence demonstrating nonadrenergic, noncholinergic mechanisms involved in lower urinary tract function. The neuropeptides implicated include vasoactive intestinal polypeptide [2, 16, 18–20, 22, 41, 46, 48, 55, 64, 69, 75], substance P [16, 19, 41, 47, 96], calcitonin gene-related peptide [22, 107], adenosine 5'-triphosphate[3, 46], somatostatin [16, 19, 48, 75], neuropeptide Y [41, 70] [17, 75], enkephalin [16, 48, 54, 96], nitric oxide [4, 40], and many others [16, 22, 27, 46, 53, 101]. These neuropeptides have been demonstrated within the detrusor/urethral wall, pelvic ganglia, and central nervous system (see Table 1). A detailed review of this topic is beyond the scope of this chapter and the reader is referred to de Groat [22] for an excellent summary.

The intricate coordination of peripheral factors and the central nervous system allow the storage of urine at low pressures with maintenance of continence and efficient bladder emptying. The complex tasks of the lower urinary tract are facilitated by anatomic, neurologic, and physiologic features which are highly specific to its function. A basic understanding of the normal physiology of the lower urinary tract is essential to interpret abnormal bladder function and apply therapeutics in the management of bladder dysfunction.

Throughout the twentieth century progressively sophisticated research tools have been able to uncover the incredible complexity inherent in maintaining normal lower urinary tract function. As these trends continue new research models involving intracellular and genetic factors will enhance our knowledge of workings of these organs even more. The horizon for pushing back the frontiers of ignorance continue to burn brightly.

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Table 1. A summary of neurotransmitters and/or neuromodulators described within the lower urinary tract. *ACh* acetylcholine, *ATP* adenosine 5'-triphophosphate, *CGRP* calcitonin gene-related peptide, *DBH* dopamine β-hydroxylase, *DYN* dynorphin, *ENK* enkephalin, *NPY* neuropeptide Y, *NOS* nitric-oxide synthase, *NA* noradrenaline, *5-HT* serotonin, *SOM* somatostatin, *SP* substance P, *TH* tyrosine hydroxylase, *VIP* vasoactive intestinal peptide

Location	Preganglionic	Cell bodies	Postganglionic	Sensory
Inferior mesenteric ganglion	ACh, ENK	NA, DBH, NPY±TH, SOM	NA, NPY, ATP	SP, CGRP, VIP
Pelvic plexus	ACh, ENK	ACh, VIP, NA, DBH±NA, NPY±NA, ENK, SOM, DYN, 5-HT	ACh, VIP, NA, NPY	SP, CGRP, VIP
Detrusor	ACh, ENK	ACh, VIP, NPY, SOM, ATP, DBH–NA, NOS	ACh, VIP, NPY±NA, NA, NOS	SP, CGRP, VIP
Trigone and ureterovesical junction	ACh, ENK	NPY, VIP, ACh, NA, NOS	NA, DBH, NPY, VIP, ACh, NOS	SP, CGRP, VIP
Bladder neck and urethra	ACh	NPY, VIP, ENK, SOM, NOS	NA, NPY, ACh, VIP, ENK, NOS, SOM, 5-HT	SP, CGRP, VIP
External urethral sphincter	–	NPY, VIP, SOM	–	–

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Epidemiology of Neurogenic Bladder Dysfunction in Children

3

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3.1
Introduction

A normal urinary bladder accomplishes two major tasks: urine storage in a low-pressure system and urine release, through a low-resistance system. Neurogenic bladder dysfunction (NBD) is a term that summarizes all kinds of bladder malfunction, resulting in urinary retention or incontinence, or a combination of both. Different classifications concerning NBD exist: etiological (congenital or acquired); anatomical (neurological level); and pathophysiological (detrusor–sphincteric coordination) In children the classification can be divided into congenital or acquired NBD (Table 1).

Achieving continence, ensuring storage, and protecting the upper urinary tract remain major goals in the treatment of children with neurogenic and/or anatomical voiding dysfunction. Prior to 1970, treatment consisted of indwelling catheters, external collection devices, or incontinent urinary diversion. A significant advancement came with the introduction of clean intermittent catheterization (CIC). The CIC alone or combined with pharmacotherapy allows up to 81% of these patients to be dry.

In this chapter we evaluate epidemiological data concerning affected children from diagnosis to adult age.

3.2
Congenital Spinal Dysraphism

In the past myelodysplasia was the most common cause of NBD in children. A failure of the neurulation process, during the early period of the pregnancy (fourth and fifth weeks), may induced different abnormali-

Table 1. Classification of principal causes of neurogenic bladder dysfunction (NBD) in children

Congenital	Spinal dysraphism	Spina bifida
		Sacral agenesis
		Tethered cord
	Cerebral palsy	
Acquired	Spinal cord lesions	Neoplasm (neuroblastoma compression)
		CNS infection or degenerative disease
	Neurological pelvic injury	Severe pelvic traumatism
		Extensive pelvic surgery

Table 2. Classification of closed cranial and spinal dysraphism

Closed cranial dysraphism	Closed spinal dysraphism
Anencephaly	Spina bifida aperta (cystica)
Encephalocele (meningocele or meningomyelocele)	Myelomeningocele
Craniorachischisis totalis	Meningocele
Congenital dermal sinus	Myeloschisis
	Congenital dermal sinus
	Lipomatous malformations (lipomyelomeningoceles)
	Split-cord malformations
	Diastematomyelia
	Diplomyelia
	Caudal agenesis

ties called neural tube defects (NTD). A embryological classification identified two groups: (a) precocious failure of the primary neurulation inducing an open NTD with exposure of neural tissue and a concomitant cerebrospinal leakage; and (b) secondary neurulation defect inducing a closed NTD. In this form, the neural tissue is covered by a normal or dysplastic skin.

Closed dysraphisms are a group of different congenital defects involving the neuro-vertebral axis, including musculo-cutaneuos covering resulting from the embryogenic perturbation of ectoderm, neuroectoderm, mesoderm, and entoderm (Table 2) [38]. At birth the closed dysraphism is more common in girls than in boys [21].

The most affected spinal levels are lumbar (40–45%) and thoraco-lumbar (26%); both sacral and lumbo-sacral represent about 10–15% of cases. The prevalence of closed spinal dysraphism (CSD) varies dramatically by different continent, region, race, and ethnicity, but most of all by time period [21, 22, 23, 25, 26, 28, 39–41]. Continent and different region of the same continent, as well as some time period differences, are reported in Table 3.

Major differences are present between continents and different countries of the same area. For example, in the U.S., spina bifida rate for all births was 1/10,000 in Alaska and 9.3/10,000 in Arkansas during the same year (1996). In Europe, the rates in Ierland and Malta for all births with covered spinal defects was the greatest with 4.7 and 4.68/10,000 in 2000 [20, 25]. The highest incidence in South Africa and South America is probably related to poor nutritional condition.

For the past 10 years, the incidence of myelodysplasia has been steadily decreasing [21–23, 26, 28, 42, 43] because of early detection in the antenatal period (sonography and screening of maternal serum alpha-fetoprotein), resulting in termination of the pregnancy.

A recognized chromosomal, teratogenic, or Mendelian malformation syndrome can be identified only in a small proportion of individuals with meningomyelocoeles [21, 46].

Estimation of CSDs worldwide and in most of the industrialized countries is also related to the availability of prenatal diagnosis and consequent elective termination of affected fetuses [21]. The decreasing incidence and difference between live birth and stillbirth in the U.S. during the past 6 years are reported in Tables 4–6 [29, 45].

Another reason for decreasing incidence is the prevention by folates administration in women: 400 µm of folic acid before conception and during early pregnancy significantly reduces the birth prevalence of NTD [23].

A study from the United Kingdom, however, found that the birth prevalence of NTDs started to decrease before folic acid recommendation was introduced, probably related to improved maternal nutrition and changed fertility patterns [23, 44].

Occult spinal dysraphism (OSD) must also be cited. The real incidence is unknown, but about 40% of the detected cases present urological symptoms at the diagnosis [33].

Over 50% of the population with spina bifida demonstrate signs of significant upper urinary tract dysfunction [22]. Neuropathic bladder effects have been detected before birth [1]. At birth and during early months, a changing pattern is often seen in the urodynamics [2, 24]. Upper motor type and lower motor type dysfunction are reported with about the same incidence, and even though rare, also a mixed type (upper and lower) may be observed [27].

Some patients experience renal scarring, sometimes at presentation, with renal impairment [24]. The most frequent modifications in the urinary tract are bladder capacity, bladder pressure, post-micturition residue, detrusor–sphincter dyssynergia, detrusor hyper-reflexia, open bladder neck, and vesicoureteric reflux [31]. The consequent renal damage from recurrent UTIs may cause chronic renal failure, which is the leading cause of death in patients with CSD [30, 35]. In adulthood about 58% of deaths in patients affected by CSD occur between 16 and 30 years of age [35], and the most important morbidity factors with renal complication are hydronephrosis 34% and kidney stones 19.6% [35]. The most affected kidney with decrease in renal function are the female kidneys, and the same vulnerability exists in patients with idiopathic vesicoureteral reflux (VUR) but without CSD[36].

Even if a minor difference exists between idiopathic and affected CSD patients in the incidence of chronic pyelonephritis (50 and 56%, respectively), the urody-

Table 3. Differences in incidence of neural tube defect (*NTD*) between geographic areas with regard to all pregnancies, but also stillbirths and live births, monitoring also what happens about death in uterus and terminated pregnancies. *CSD* closed spinal dysraphism

Region	All pregnancies	Total birth	Stillbirth	Live birth	Live birth CSD
Canada[a]	1991/10.0				
	1995/9.2				
	1999/5.8				1999/4.0
Ontario	1986/11.7		2	8.6	
	1995/16.2				
	1999/8.6		1	4.3	1999/4.7
Alberta					1999/3.0
Quebec					1999/3.8
British Columbia					1999/5.9
Nova Scotia					1999/6.1
United States[b]	1996/1.0-9.3[b]				
		2000/4.16			
Mexico 2000		19.07			
Europe 2000					Live birth+stillbirth CSD
Czech Republic	9.6				1.86
England and Wales	7.7				1.37
Finland					2.63
France					
Central east	6.8				0.28
Paris	17.5				1.02
Strasbourg	14.2				1.40
Germany Saxony-A	15.90				2.13
Hungary	4.1				1.63
Ireland					4.7
Italy					
Northeast	7.78				1.63
Central (Tuscany)	8.26				1.51
Central (Emilia-R)	7.24				0.81 (all pregnancies 4.43)
Central–south (Campania)	9.3				2.79
South (Sicily)	13.0				3.27
Malta					4.68
Northern NL					4.40
Norway	12.21				3.86
Russia (Moscow)	11.50				4.88
Spain ECEMC*					1.70
Sweden					1.76 (all pregnancies 5.49)
South Africa		18.93			
South America		19.60			
United Arab Emirates		9.78			
South Australia					1990–1991/2.5
China 1992–1994					
North	34.4				
South	7.2				
Japan 2000		5.13			
New Zealand 2000		4.04			

[a] From [26], [b] From [25], *ECEMC = Estudio Colaborativo Español de Malformaciones Congenitas. Spanish Collaborative Study Of Congenital Malformations

Table 4. U.S. rate of live births with spinal bifida only. (From [29])

Year	Rate
1995	2.8
1996	2.64
1997	2.47
1998	2.24
1999	2.07
2000	2.08
2001	2.01

Table 5. U.S. rate of live+stillbirth with spina bifida only. (From [29])

Year	Rate
1974–1979	7.16
1980–1984	6.61
1985–1989	5.65
1990–1994	3.40
1995–1999	2.34
2000 (incomplete)	1.98

Table 6. U.S. rate difference between live birth and stillbirth

Live birth	Stillbirth
Spina bifida (75%)	Anencephaly (57%)
Encephalocele (15%)	Spina bifida (35%)
Anencephaly (11%)	Encephalocele (7%)

namic pattern in children with CSD is an evolving one, and renal damage becomes progressive [36]; 40% of the patients with a neurogenic bladder due to CSD underwent a surgical procedure to the urinary tract [35]. Videourodynamic study is strongly recommended and considered as the gold standard for extended diagnosis, and urodynamic disorders are found in more than 90% of the patients with CSD, demonstrating abnormal innervation of the bladder [27, 28].

A bladder pressure more >40 cmH_2O is the essential urodynamic warning for the upper urinary tract damage [3].

Achieving continence is another goal in the treatment of these children, until adulthood. The CIC alone or combined with oral therapy allows up to 81% of these patients to be dry [31, 49, 48], even if about 60% of the affected patients are incontinent when adult [32].

3.3
Spinal cord injury

Spine Cord Injuries (SCI) are rare in the pediatric population: 2–5.5% of all patients with spinal cord injuries (SCIs) [4]. Even if infrequent, SCI in the pediatric population represents about 25,000 new cases every year in North America and Europe, often with consequent neurogenic bladder. This means that about half a million children between 0 and 16 years of age have been affected by neurogenic bladder following a SCI in the past 20 years on those two continents.

Early pediatric SCI studies revealed upper tract changes in 31–43% of the patients with a spine injury [17–19]. In the past, the leading cause of death among persons with SCI was renal failure. Presently, significant advances in urological management (CIC, anticholinergics, advancement in surgical technique) decreases urinary damage, resulting in shifts in the leading causes of death [5]. Urinary tract infections (UTI), hydronephrosis, vesicoureteral reflux, lithiasis, and renal scarring, or other genito-urinary complications, represent about 4% of all causes of death (ICD9CM codes: 580-629), which means renal failure is the eleventh primary cause of death [5]; however, a urinary incident is the first cause of rehospitalization: about 28% occurred during the first year after injury, 34% 10 years after, and approximately 37% 15 years after the injury [5].

Epidemiological data regarding aetiology and physiopathology of SCI must be considered to evaluate social impact life expectancy and urinary tract management.

3.3.1
The Frequency Distribution of Age at Injury

In the U.S. about 53% of all injuries occured between ages of 16 and 30 years, but only 4.4% between ages of 0 and 16 years, in which only <0.1% are under 1 year of age [5, 7]. About 40 cases per million population in the U.S. and Japan [10] correspond to the annual incidence of SCI. In Europe, and in Italy in particular, the annual incidence is about 20 cases per million population, and only 2% occurs in pediatric patients [5, 6, 8].

3.3.2
Etiology at the Age of Injury

Etiology at the age of injury is different with different pathological implications concerning the mechanism and spinal level. The three most representative categories are [5, 9, 12]:

1. Vehicular accidents (auto, motorcycle, all terrain vehicle = ATV/all terrain cycles = ATC, boating mishaps, accidents involving fixed and rotating wing aircraft, snowmobile, and bicycling accidents)
2. Sports groups
3. Violence (gunshot and other wounds, personal contact injuries, and explosions)

Although falls generally represent the leading cause of mortality and morbidity in children in the U.S., only 2% of all falls result in a spinal injury or SCI with or without fracture [13]. The SCI without radiographic abnormality (SCIWORA) represents 15–25% of all pediatric SCI, with a high rate (about 32%) in young children under 8 years, and only 16% in older children.

Other possible traumatic etiologies are reported in the pediatric population, such as complication secondary to surgery for spine deformation (2–3% postoperatively), or neurosurgery in which a spinal cord vascular injury is an unusually catastrophic complications, and exeptional hematoma secondary to hemostatic disorders (hemophilia).

3.3.3
Anatomical Level of the Injury

In data from U.S., from 60% to 80% of all SCIs among pediatric age occured in the cervical segment, whereas that location represents about 30–40% in adults SCIs [14]. The urodynamics outcome depended on the level lesion (above the sixth thoracic vertebra or below the sixth thoracic vertebra) [15].

Above the sixth thoracic vertebra, patients may have an intact sacral reflex arc, and most often only a detrusor hyperreflexia. A unique complication of T6 injury is autonomic dysreflexia [15].

Below the T6 level, spinal cord lesion patients will have urodynamic findings of detrusor hyperreflexia, and non-coordination striated sphincter dyssynergia, with a high damage risk for upper urinary tract. The risk of UTI and renal failure is higher in this second group [11, 15].

Bladder status in patients with complete suprasacral lesion is spastic in 100%. Conversely, 100% of flaccid bladders are present in patients with complete sacral lesion.

The differences in the bladder status concerning patients with sacral and suprasacral incomplete cord lesions are reported in fig 3.1 [15, 16].

3.3.4
Bladder Compliance

There is a difference in managment and diagnostics of the urinary tract in those patients with low bladder compliance compared with patients with normal bladder compliance. Differences were found among cervical, thoracic, and lumbar SCI; in particular, they concern hyperreflexia, safe capacity (SC), and expected capacity (EC) of the bladder (Fig 3.2). The incidence of hydronephrosis is about 64% and vesicoureteral reflux is about 46% in pediatric patients with post-injury low compliance, compared with 21 and 6%, respectively, in pediatric patients with normal compliance [17].

Table 7. Bladder and sphincter dysfunction are much more frequent in the lower neurogenic lesions. *CIC* clean intermittent catheterization

	Cervical	Thoracic	Lumbar
Average age at injury (years)	4.8	5.9	3.4
CIC (%)	80	96	100
Dry (%)	80	54	33

The importance of the SCI level is also uderlined by bladder management, which can lead to different results in the different groups (Table 7) [17]. Data in the literature are not consistent. Statistical significance must be confirmed in most of the cases.

3.4
Cerebral Palsy

Neurological damage in cerebral palsy (CP) may cause a delayed or incomplete development of bladder control. Several impairments in communication, cognition, upper arm function, and mobility are also characteristic in these patients, and together with neurological damage may result in transitory or permanent urinary incontinence.

The development of bladder control in children with CP is delayed in comparison with normally developing children. Even if later the development of the bladder control does occur similar to that in the normal children, diurnal dryness occurs first, and nocturnal dryness is achieved in the majority of the cases some years later [56, 59].

Considering individuals with spastic tetraplegia and/or low intellectual capacity, a chance of achieving continence is possible in 39–58% of cases before the age of 8 years and even occurs in older children [56]. For children with urinary incontinence who are 8 years old and who have a high mental capacity as well as spastic hemiplegia or diplegia, 85–92% can achieve bladder control and continence spontaneously [56, 58].

Physiopathological studies report detrusor muscle hyperreflexia in all the patients, but also deficit of vesicourethral sensation and detrusor–sphincter dyssynergia have been observed [60, 57]. These functional fin-

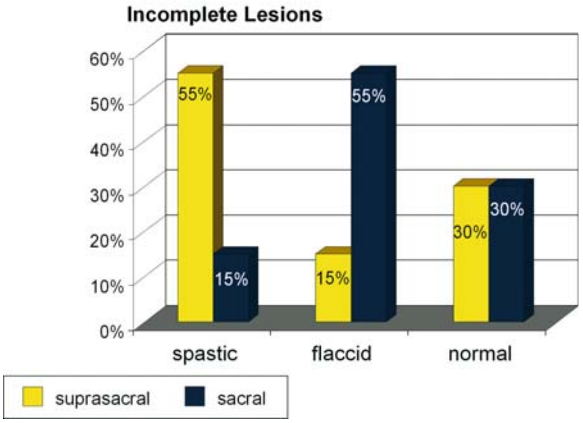

Fig. 1. incidence of bladder dysfunction in patients with incomplete spinal lesions. Difference with complete lesions: 30% of normal cases are possible.

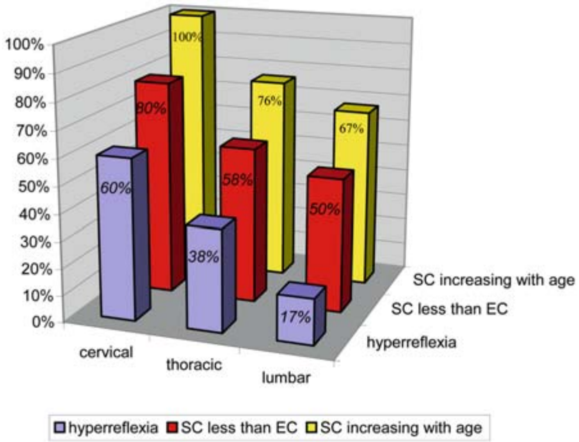

Fig. 2. different percentage of hyperreflexia and bladder capacity related to the injury site. SC = safe capacity, EC = expected capacity

dings are compatible with an upper motor neuron lesion which is the cause of altered bladder emptying, and consequently, urinary tract complications [57].

The literature reports 86% of evidence of a pure upper motor neuron injury, but in only 11% of the children electromyographic findings suggest an incomplete lower motor neuron sphincteric injury [58]. A urodynamic study reported a reduced compliance in 91% of the CP and in 70% of the patients an increased leak-point pressure (LPP) [59], but progressive urinary tract deterioration remained uncommon because of a conservative detrusor–sphincteric synergia.

3.5

Anorectal Malformations

The associated urological disturbances in anorectal malformations (ARM), particulary in high ARM and cloacal malformations, is well known. They are explained by various possible abnormalities: associated CSD (sacral agenesis, tethered cord), and operative neurological or urethral injury, but also urinary-tract-associated malformation including VUR, hydronephrosis, and renal agenesis.

The overall incidence of spinal cord abnormalities in patients born with ARM has been reported in different series to be 9.8–60%, but in cloacal malformation it is close to 90% [61, 65, 67, 52].

The incidence of urogenital malformations in these patients varies from 20 to 54%, particularly in high ARM; in these the VUR frequency is between 33 and 47% [65]. The rate of neurogenic voiding dysfunction (NVD) is reported to be from 5.7 to 45% [34, 64, 65]. The majority of the NVD cases occur in the high-ARM group. When considering only the high-ARM group the frequency of NVD rises to 80% [65], but it is also reported that about 80% of the male patients with low lesion associated with a tethered cord, and only 37% of the female patients, show the same abnormality [52, 68].

An NVD may be present in the absence of any recognizable sacral/spinal abnormalities [67]. It is believed to be related to a neural tissue insult during embryogenesis [68], long before surgery. Table 8 summarizes the different possibilities and percentages, explaining the high risk of NBD in patients with ARM [67]. It is accepted that lower urinary tract dysfunction in ARM does not directly depend on PSARP surgical correction, regardless of the level of rectal pouch [61, 66, 65].

Urodynamic and videourodynamic studies should be carried out in all patients with ARM, especially in children with initial uroradiographic abnormality, or in those with recurrent urinary tract infections. The LPP study shows an average of 74 cmH_2O in patients with ARM. These data remain essentially unchanged before and after surgical correction [61]. It is important to remark that also in some patients with normal spinal imaging studies, elevated LPP is observed. A normal spinal evaluation does not exclude the possibility of NVD that eventually may be harmful to the upper urinary tract [62]; the liter-

Table 8. Normal spinal cord associated with normal urodinamic finding is reported in only 20% of the patients.

		Normal urodynamic findings	Pathological urodynamic findings
Normal spinal cord (%)	43	20	23
Spinal cord abnormalities	57	23	34

ature reports 6–10.8% of overactive detrusor and 2.1–6% of inactive detrusor in patients without sacral anomalies [61, 66]. It must be remembered that urological failure still represents the most important causes of morbidity and mortality in patients with ARM malformation [63].

3.6
Pelvic Surgery: Teratoma and Other Pelvic Tumor Resection

3.6.1
Sacrococcygeal Teratoma

Urological complications are observed in 22–28% of the patients' follow-up SCT resection [54]. Urological sequelae are mostly related to the type of the position and not to malignant spread of the tumor; 85% of the type-IV SCT (presacral), 12.5% of type II, and 10% of type I have postoperative incidence of a neurobladder dysfunction [54].

Poor bladder emptying, elevated intravescical pressure with hydronephrosis, and bladder trabeculation are present in 21% of the patients preoperatively, and in 10.5% postoperatively [55]. Prenatally detected urological abnormalities are usually related to direct obstruction, whereas malformations of the renal tract are not increased [51]. Expansive tumor growth can permanently damage pelvic floor musculature leading to functional impairment of sphincter structures [53]. Tethered cord and neurological lesion related to the tumor are also observed [53]; however, the most common cause of bladder dysfunction appears secondary to surgical damage of the pelvic plexus nerve. The incidence of vesical dysfunction after SCT appears too high in comparison with other surgical interventions in the pelvis to accept the surgical trauma as the only cause [51].

All the aspects of NBD are found in SCT sequelae, emptying, synergy, and voiding disturbance, and the frequency is reported in Table 9 [53].

For the many disturbances, clean intermittent catheterization is the best initial management, and most of these patients return to a normal bladder function within 45 days; however, all patients with large sacrococcygeal teratoma should undergo long-term urological follow-up.

Table 9. Urodynamic pattern and urinary incontinence

Detrusor dysfunction	73%
Sphincter disfunction	54.4%
Dyssynergia	36.4%
Incontinence	82%

Table 10. Percentage of RMS versus all kind of pelvic mass comparing different arising site

Site of rhabdomyosarcoma	All RMS in children (%)
Genitourinary	21
Pelvic	6
Retroperitoneal	5
Perineum perianal	2

3.6.2
Other Pelvic Tumors

The most common pelvic tumor in children is rhabdomyosarcoma, which represents about 4–15% of all pediatric malignant solid tumors [70, 69]. Early non-invasive urodynamic study is always recommended, and when a urinary dysfunction appears, a pressure-flow urodynamic study is mandatory. Rhabdomyosarcoma can arise from bladder, prostate, uterus, vagina, vulva, and non-genitourinary pelvic tissues [71] (Table 10).

Other tumors with pelvic localization in pediatric age (excluding SCT) are pelvic neuroblastoma (pelvic incidence 5% of all NBL) [82], germ cells tumors, lymphoma, ovarian teratoma (the pelvis is the site of 78% of childhood teratomas with 43% in the ovaries) [78], osteosarcoma of the pelvis (4% of all osteosarcoma in children) [81], and other rare tumors in the pelvic region such as PNET or Ewing's sarcoma.

Neuroblastoma is the most common malignant cause of spinal compression in the pediatric population. In prolonged medullary neuroblastoma, 52% of the patients show neurological symptoms at diagnosis, but after treatment only 20% still present neurogenic symptoms [50]. In a French NBL-90 study and NBL-94 study (46 patients), chemotherapy improved partial neurological deficits in 92% of cases, and obviated decompressive laminectomy in 60%; 15% suffered severe sequelae [79].

Improving chemotherapy for all of these pediatric tumors has resulted in a changed role for the surgeon. Less radical resection of these tumors is presently indicated and performed. The aim is to preserve physiology of urinary, fecal, and sexual function which depends on preservation of S3 and, above all, innervation (Table 11). Precise histological and genetic identification of the tumor, and the specific anatomic location and extent of the tumor in the pelvis, are involved in surgical strategy [82].

Although very rare osteosarcoma of the pelvis is described also in pediatric age, in these cases pelvic surgery can result in damage to the pelvic splanchnic nerves, hypogastric nerves, and the pelvic nerve plexus, and differ-

Table 11. Pediatric pelvic tumor resection without bladder resection

Reference	No. of patients	Alive with bladder salvage (%)
[72]	161	22 – 23
[73]	25	16
[74]	15	53
[75]	15	26
[76]	9	77
[77]	10	60
[69]	11	18

Table 12. Denervation risk and urinary consequence

Injury site	Denervation	Urinary tract dysfunction
Splancnic nervs S2–S4	Parasympathetic	Areflexic bladder
Hypogastric nerves and plexus (aortic bifurcation)	Sympathetic	Loss of bladder compliance and neck competence
Pelvic plexus	Mixed pattern	Bladder–sphincter–urethral dysfunction

ent patterns of dysfunction are observed due to denervation of the lower urinary tract (Table 12) [80, 82].

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Pathophysiology of Neurogenic Bladder Dysfunction

4

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4.1
Introduction

Although the prevalence of children with a neurogenic bladder dysfunction due to spina bifida has decreased (prenatal diagnosis and the use of folic acid supplements during pregnancy), there are still many children presenting with signs of a neurologic lesion of the detrusor and/or sphincter mechanism.

Management of neurogenic detrusor sphincter dysfunction in children has undergone major changes over the years. While the use of diapers, permanent catheters, external appliances and various forms of urinary diversion were acceptable treatment modalities, these are now reserved for only a small number of patients [1].

Initially long-term renal preservation was the only aim of therapy and early diversion had the best long-term results for preserving renal function. Despite some of the complications of ileal conduits and cutaneous urostomies requiring secondary surgery, this form of treatment offered the best outcome for renal preservation with socially acceptable continence [2].

Introduction of clean (self) intermittent catheterization revolutionized the management of children with neurogenic bladder. It not only made conservative management a very successful treatment option, but it also made surgical creation of continent reservoirs a very effective alternative with a good quality of life [3].

Neurogenic bladder dysfunction in children with myelodysplasia presents with various patterns of detrusor–sphincter dysfunction within a wide range of severity. About 15 % of neonates with myelodysplasia have no signs of neuro-urologic dysfunction when initially studied [4]; however, there is a high chance of progressive changes in the dynamics of the neurologic lesion in time and even babies with normal neuro-urologic function at birth have a one in three risk of developing either detrusor–sphincter dyssynergia or areflexia by the time they reach puberty [5].

At birth the majority of patients have normal upper tracts, but nearly 60% of them will develop upper tract deterioration due to increased detrusor filling pressures and infections, with or without reflux [6, 7].

As our understanding of urodynamic studies has evolved, it has allowed us to understand the nature and severity of the problems and administer management in a more rational manner differing from one patient to the other. Although the last quarter century has witnessed remarkable progress in the management of these children, the main goals of treatment have remained the same, i.e., the prevention of urinary tract deterioration and the achievement of continence at an appropriate age.

4.2
Presentation of Neurogenic Detrusor Sphincter Dysfunction in Children

Neurogenic detrusor sphincter dysfunction can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or the peripheral nervous system.

The most common presentation is at birth with myelodysplasia. The term “myelodysplasia” includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children.

The neurologic lesions produced by myelodysplasia are variable contingent on the neural elements that have everted within the meningocele sac. The bony vertebral level correlates poorly with the neurologic lesions produced. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion and scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth.

In occult myelodysplasia the lesions are not overt and often with no obvious signs of neurologic lesion, but in many patients, a cutaneous abnormality overlies the lower spine. This can vary from a dimple or a skin tag to a tuft of hair, a dermal vascular malformation, or an obvious subdermal lipoma. Alterations may be found in the arrangement or configuration of the toes, along with discrepancies in lower extremity muscle size and strength with weakness or abnormal gait. Back pain and an absence of perineal sensation are common symptoms in older children. Incidence of abnormal lower urinary tract function in patients with spina bifida occulta is as high as 40%. Occult lesions may also become manifest with tethering of the cord later in life. This can lead to changes in bowel, bladder, sexual and lower extremity function.

Sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. Perineal sensation is usually intact and lower extremity function is usually normal and the diagnosis is made when a flattened buttock and a short gluteal cleft is seen on physical examination. This lesion may produce variable degrees and patterns of voiding dysfunction.

Cerebral palsy patients may also present with varying degrees of voiding dysfunction usually in the form of involuntary detrusor contractions and wetting.

4.2.1
Imperforate Anus and Cloacal Malformations

Up to 40–60% of children born with these abnormalities have a neurogenic bladder dysfunction. There is a strong correlation between sacral and vertebral abnormalities and the detrusor-sphincter dysfunction. Because extensive surgical procedures are usually necessary to correct the abnormality, it is sometimes difficult to predict the outcome of bladder function. Pre-operative urodynamic evaluation may be helpful, but probably the best predictive factor is radiological evaluation of the sacrum and spinal column.

Detrusor sphincter dysfunction is poorly correlated with the type and spinal level of the neurologic lesion.

4.3
Classification: Pattern Recognition

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of the neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurologic disease or injury. Such systems are based on the localization of the neurologic lesion and findings of the neuro-urologic examination. These classifications have been of more value in adults, as neurogenic lesions are usually due to trauma and more readily identified.

In children the spinal level and extent of congenital lesion is poorly correlated with the clinical outcome. Indeed, severe detrusor-sphincter dysfunction has been associated with minimal bony defects. Various possible neuropathologic lesions of the spinal cord, including syringomyelia, hydromyelia, tethering of the cord, and dysplasia of the spinal cord, are the causes of these disparities, and they may actually extend several segments above and below the actual site of the myelomeningocele. Therefore, urodynamic and functional classifications have been more practical for defining the extent of the pathology and planning treatment in children.

The detrusor and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction. Determined by the nature of the neurologic deficit, they may be either in an overactive or in an inactive state. The bladder may be overactive with increased contractions, have diminished capacity and compliance, or be inactive with no effective contractions. The bladder outlet (urethra and sphincter) may be independently overactive causing functional obstruction or paralyzed with no resistance to urinary flow. These conditions may exist in any combination [8–13].

Urodynamic evaluation (preferably in combination with fluoroscopy) makes pattern recognition possible. Four major types are usually used to describe the detrusor-sphincter dysfunction:

1. Detrusor overactivity with overactivity of the sphincter (mostly dyssynergia)
2. Detrusor overactivity with normal or underactivity of the sphincter
3. Detrusor underactivity with sphincter overactivity
4. Detrusor underactivity with sphincter underactivity

Besides these four patterns, one can use the ICS classification: overactive detrusor; underactive detrusor; overactive sphincter; and underactive sphincter. Sometimes this is more helpful, as the detrusor may be overactive during filling, but underactive during “voiding.”

Urodynamic investigations make it possible to establish a management plan for each individual patient. For the very young child the combination of an overactive detrusor and sphincter is potentially dangerous because of the high intravesical pressures, which puts the upper tract at risk (vesicoureteral reflux and hydronephrosis), whereas an inactive detrusor and paralyzed sphincter is relatively safe, providing a low-pressure reservoir [14, 15].

4.4
Pathophysiology and Management

The urologic problems in children with a neurogenic bladder are either associated with high intravesical pressures or insufficiency of the sphincteric mechanism. In the first years of life the kidneys are highly susceptible to back pressure and infection. In this period emphasis is on documenting the pattern of neurogenic detrusor-sphincter dysfunction and assessing the potential for functional obstruction, and whether or not there is vesicoureteral reflux [16, 17]. Ultrasound studies and a VCUG to exclude reflux have to be performed soon after birth. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or vesicoureteral reflux, and can help identify children at risk for upper urinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks and needs to be repeated at regular intervals, in combination with evaluation of the upper tracts [18].

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has lead to a consensus that children do not develop upper tract deterioration when managed early with clean intermittent catheterization (CIC) and antimuscarinic medication [18–21]; therefore, initial treatment should consist of oral or intravesical antimuscarinic drugs in combination with CIC, to start soon after birth in all babies and especially in those with signs of possible outlet obstruction [22–26].

The early initiation of intermittent catheterization in the newborn period makes it easier for parents to master it and for children to accept it as they grow older [27, 28].

With early management, not only are upper tract changes less, but also bladders are better protected and incontinence rates are much lower.

It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia cause secondary changes of the bladder wall. In these patients the sphincter first acts like a functional obstruction, but after some time the same changes occur as in an anatomical outflow obstruction. In that respect these bladders react in the same way as in boys with posterior urethral valves. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance, resulting in a small non-compliant bladder with progressively elevated pressures. It is believed that early institution of intermittent catheterization and anticholinergic drugs may prevent this in some patients [29–31]. Retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with early start of CIC [22, 23].

The CIC alone, when begun in infancy, can achieve continence at a rate of 60%. When combined with newer and more potent antimuscarinic drugs, continence rates approach 75–80%.

At present, oxybutynin, tolterodine, trospium, and propiverine are the most frequently used drugs: some clinical studies are available, but no randomized placebo-controlled studies have been performed [31–35].

A prospective controlled trial evaluating trospium in children reports that trospium is effective and safe in correcting detrusor instability in children, but this study does not include patients with a neurogenic bladder [36].

Use of medication in children with neurogenic bladder to facilitate emptying has not been studied well in the literature. Few studies investigating the use of alpha-adrenergic blockade in children with neurogenic bladder report good response rates, but they are non-controlled studies and long-term follow-up is lacking [37].

Use of lidocain intravesically has been shown to be effective to improve bladder capacity and compliance and decrease overactivity in children with neurogenic bladder [38]. In neurogenic bladders that are refractory to antimuscarinics and still remain to be in a small-capacity and high-pressure state, injection of botulinum toxin into the detrusor has been introduced as a new treatment alternative [39, 40]. Initial promising results in adults have also initiated its use in children. Thus far, pediatric studies have been open-label studies and prospective controlled trials are lacking [41, 42]. Injection of botulinum toxin in therapy-resistant bladders seems to be an effective and safe treatment alternative. This treatment seems to be more effective in bladders with evidenced detrusor overactivity, whereas non-compliant bladders without obvious detrusor contractions are unlikely to respond to this treatment.

Intravesical electrical stimulation of the bladder was introduced more than four decades ago and it has been tested in some open clinical trials in children since 1984. Its practice is limited to a few centers that have reported varying results. The nature of this type of treatment (time-consuming and very dedicated personnel) does not make it attractive for the majority of treatment centers.

Children with neurogenic bladder also have disturbances of bowel function. Fecal incontinence in these children is frequently unpredictable. It is related to the loss of lower bowel sensation and function, reflex activity of the external sphincter, and the consequent failure to fully empty the rectum [43].

The majority of children with a neurogenic bladder also have constipation and this is managed most commonly with laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel-emptying regimen is often necessary to maintain fecal continence, and this may have to be started even at a very young age. With antegrade or retrograde enemas, the majority of these children's constipation can be managed and they may attain some degree of fecal continence [44–48].

Biofeedback training programs to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management program in achieving fecal continence [49].

Electrostimulation of the bowel may also offer a variable improvement in some patients [50]. Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, patients with urinary tract infections should be treated only if symptomatic. There is strong evidence not to prescribe antibiotics to patients with bacteriuria without clinical symptoms [51–53]. Bacteriuria is seen in more than half of the children on CIC, but patients who are asymptomatic do not need treatment.

Patients with vesicoureteral reflux often should be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [54, 55].

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. Patients with myelodysplasia have sexual encounters, and studies indicate that at least 15–20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term; therefore, counseling patients regarding sexual development is important in early adolescence.

Children with a good response to antimuscarinic treatment and an overactive sphincter may be continent in between catheterizations. Bladder pressure and (normal) development of the upper tracts will determine whether additional treatment is necessary.

Children with therapy resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need additional surgical treatment such as bladder augmentation. Children with detrusor overactivity, but with underactive sphincters, will be in better shape in terms of protecting their upper tracts, but they may be severely handicapped because of their incontinence. Initial treatment will be intermittent catheterization (as it may reduce the degree of incontinence and offers a much better control over urinary infections) in combination with antimuscarinic drugs. At a later age the outlet resistance has to be increased in order to render them continent [56]. There is no medical treatment of proven efficacy that increases bladder outlet resistance. Alpha-receptor stimulation of the bladder neck has not been very effective. Surgical procedures need to be considered for maintaining continence [57–61].

It is important to establish adequate bowel emptying before attempting to correct bladder dysfunction surgically or medically.

Patients with a neurogenic bladder require life-long supervision and monitoring of renal function is extremely important. Periodic investigation for upper tract changes, renal function, and bladder status is mandatory; therefore, repeat urodynamic studies are needed more frequently at younger ages and less frequently at later ages. A repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In case of any apparent changes, both in the upper and lower urinary tract, or any changes of neurologic symptoms, a more detailed examination, including urodynamics and MRI of the spine, is indicated. Renal failure can progress slowly but may occur with startling rapidity in these children.

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Genetic Risk Factors for Neural Tube Defects: Folic Acid Supplementation and Prevention of Birth Defects

5

Generoso Andria · Iris Scala

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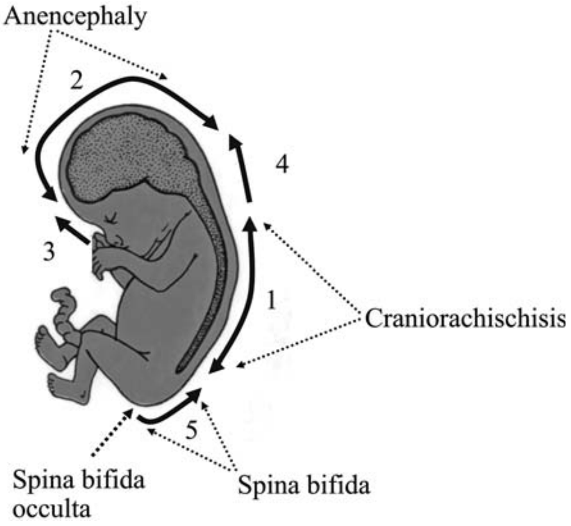


Fig. 1. Representation of multiple initial closure sites proposed for the human neurulation sequence. At least five waves of closure are proposed for normal human embryogenesis. *Closure 1* initiates at the cervical boundary and proceeds bidirectionally. *Closure 2* takes place at the forebrain–midbrain transition and, like closure 1, proceeds bidirectionally, dividing the anterior neuropore in a forebrain and a mid/hindbrain neuropore. *Closure 3* is unidirectional and proceeds caudally to meet closure 2, thereby closing the forebrain neuropore. *Closure 4* is unidirectional and meets closure 2 to close the mid/hindbrain neuropore. The posterior neuropore is closed by caudal continuation of closure 1. *Closure 5* is unidirectional and proceeds to meet closure 1. Primary neurulation is completed after the closure of this neuropore in the sacral region. The distinct types of NTD arise from failure of different closure steps.

5.1
Neural Tube Defects

5.1.1
Definition and Classification

Neural tube defects (NTDs) are severe congenital malformations resulting from failure of the neural tube to close during the first 4 weeks of human embryogenesis, with defects occurring at any point along the spinal cord, from the developing brain to the sacrum. Disorders of neural tube closure involve abnormalities in the neural tube closure junctures within cranial and caudal levels of the neural tube (Fig. 1). Defects vary in their severity, depending on the type and level of the lesion.

There are two types of NTDs. The most common type is open NTD. Open NTD occurs when the brain and/or the spinal cord are exposed at birth through a defect in the skull or vertebrae. Examples of open NTDs are spina bifida (myelomeningocele), anencephaly, and encephalocele. The most severe and common anterior defect is anencephaly, which is invariably lethal, leading to partial or total secondary brain degeneration. The exposed neural tissue is represented by a hemorrhagic, fibrotic, degenerated mass of neurons and glia, and the frontal, parietal, and squamous part of the occipital bone are usually absent. The onset is estimated to be not later than the embryonic age day 24. Neonates rarely survive more than a few hours or days. An encephalocele is the result of failure of the surface ectoderm to separate from the neuroectoderm. This results in a bony defect in the skull, which allows herniation of the meninges (cranial meningocele) or herniation of brain tissue. The occiput is the most common site of this type of NTD. Approximately 90% of cases involve the midline. The prognosis depends on the associated malformations and the size and contents of the defect. Of patients with encephalocele, 21% are born alive, but only half survive. Approximately 75% of survivors have a mental deficit. Encephalocele recurs in 3% of patients after surgical repair. The absence of brain tissue within the herniated sac is the single most favorable prognostic feature for survival.

Meningo(myelo)cele is an open spinal dysraphism deriving from an anomaly of neurulation and resulting in protrusion and exposure of the spinal cord. The terms meningocele and myelomeningocele are used according to the degree of herniation of the spinal content through the opening. The anomaly occurs within day 24 of embryonic development. Meningo(myelo)cele is evident at birth and requires immediate reparative surgery. Damage to open neural tissues is progressive and results from exposure to amniotic fluid or contact to uterine wall. The clinical spectrum of NTDs also includes craniorachischisis, in which the neural folds do not elevate to fuse along the length of the embryo, and iniencephaly, in which there is a lack of proper formation of the occipital bones, with a short neck and a defect of the upper neural tube. A rarer type of NTD is closed NTD that occurs when the spinal defect is covered by skin. Common examples of closed NTDs are lipomyelomeningocele, lipomeningocele, and tethered cord. Spina bifida occulta, the mildest form of spinal dysraphism, occurs most often at S1–S2 and is a bony defect of the spine, usually covered by skin

5.1.2
Clinical Consequences and Management

Besides anencephaly and cranial encephalocele, meningomyelocele is the most severe form of NTD, involving dysfunctions of many organs and structures such as skeleton, skin, genitourinary tract, as well as the peripheral and central nervous systems. The lumbosacral region is involved in 75% of cases; however, a meningomyelocele may be located anywhere along the neuraxis and the degree of the neurological deficit varies according to the site of the malformation. A lesion in the low sacral region causes bowel and bladder incontinence, and anesthesia of the perineal area, but not impairment of the motor function. A midlumbar lesion is often associated to flaccid paralysis of the lower extremities, postural abnormalities, absence of deep tendon reflexes, lack of response to touch and pain, urinary dribbling, and relaxed anal sphincter. The neurological deficit increases as the meningomyelocele extends to the thoracic region; however, cervical lesions usually display minimal neurological deficit and hydrocephalus in very few cases.

Hydrocephalus associated with a type-II Chiari malformation occurs in 80% of patients with meningomyelocele, requires shunting procedures and, if untreated, may cause feeding problems, stridor, and apnea secondary to cerebellar tonsil herniation through the foramen magnum. The management is multidisciplinar and involves surgeons, physicians, and therapists. With the exception of a leak of cerebrospinal fluid through the defect, surgery can be delayed for several days in order to assess the extent of the lesion, the genitourinary system function (renal function, neurogenic bladder), bowel function, and the neurological deficit. After surgical repair, the neurological deficit remains stable. The prognosis varies according to the degree of the white matter herniation, the site of the lesion and the management of urinary tract infections and of possible meningitis. Almost every child with a sacral or lumbosacral lesion can obtain deambulation.

Meningocele consists of the herniation of meninges through a defect of the vertebral arches and, thus, the neural tissue is preserved. Children are usually asymptomatic with normal neurological examination. Special attention should be paid to possible hydrocephalus, leaking of cerebrospinal fluid, and prevention of meningitis.

Spina bifida occulta is often asymptomatic, has no neurological signs, and usually has no clinical consequences. In some cases, it is indicated by patches of hair on the overlying skin, a lipoma, a discoloration of the skin or a dermal sinus, which consists of a narrow duct with a skin opening, a possible site of infection spreading (i.e., recurrent meningitis of unknown origin).

5.1.3
Prevalence

The birth prevalence of NTDs varies among countries and ethnic groups. The prevalence ranges from 1 in 150 pregnancies in northern China to 1 in 2500 in Finland. In Italy, the prevalence is 1 in 1400 pregnancies. The worldwide average prevalence is 1 in 1000. The prevalence of NTDs in early pregnancies is reported to be 10–50 times higher than at term, and the discrepancy is caused by spontaneous embryonic abortions and termination of pregnancies after prenatal diagnosis.

5.2
Embryology of Neural Tube Closure

5.2.1
The Neurulation Sequence and NTDs

The development and closure of the neural tube are normally completed within 28 days after conception, before many women are aware that they are pregnant. The closure of the neural tube occurs at several sites and the clinical types of NTDs differ depending on the site at which closure fails. Neurulation in humans occurs in two phases, a primary and a secondary neurulation phase, during which neural tube formation is initiated by neural folding and completed by canalization. Primary neurulation consists of the folding of the neural plate on the dorsal side of the embryo and the formation of the brain and spinal cord. Secondary neurulation results in the development of the most caudal part of the spinal cord through the processes of canalization and retrogressive differentiation of the neural cord.

5.2.2
Primary Neurulation

During primary neurulation, the neural tube forms through three main steps: shaping; folding; and midline fusion of the neural plate (Fig. 2). Subsequently, the surface ectoderm differentiates to cover the neural tube. The first process consists of the formation of the neural plate from the middle part of the ectoderm due to the induction by the underlying notochordal plate and prechordal mesoderm [32]. After the formation of the neural plate, the shaping process begins and the neural plate starts to bend. This involves elevation of the neural walls and the formation of the neural folds. The following process is convergence, or medial bending, of the

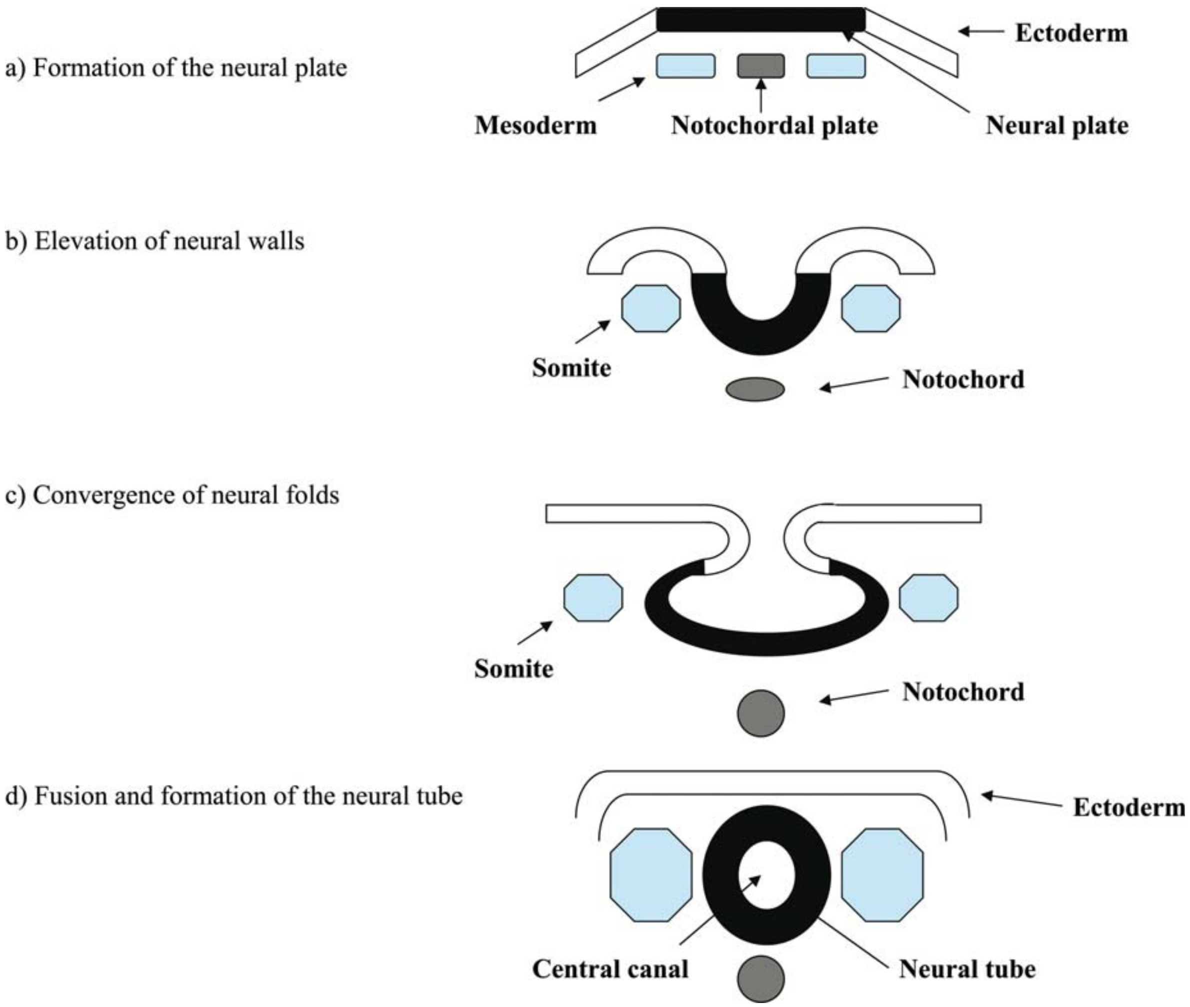

a) Formation of the neural plate
Ectoderm
Mesoderm
Notochordal plate
Neural plate
b) Elevation of neural walls
Somite
Notochord
c) Convergence of neural folds
Somite
Notochord
d) Fusion and formation of the neural tube
Ectoderm
Central canal
Neural tube

Fig. 2. Phases of primary neurulation (transverse view)

neural folds, possibly facilitated by the expansion of ectoderm. Finally, the neural tube closes through the adherence and fusion of the neural folds. Data from animal models suggest that closure of the neural tube is not a continuous process but derives from at least four different closure initiation sites plus five transient neuropores [14], as shown in Fig. 1.

5.2.3
Secondary Neurulation–Canalization

Closure of the neural tube is followed by secondary neurulation, which leads to formation of the most caudal portion of the spinal cord, including most of the sacral and all of the coccygeal regions. The junction of primary and secondary neural tube occurs at the sacral level of the embryo [31]. The caudal eminence is formed caudally to the posterior neuropore. Mesenchymal cells in the dorsal part of the caudal eminence form a secondary neural tube, whose lumen is continuous with that of the primary neural tube. The lumen of the primary neural tube proceeds caudally and makes contact with the newly formed lumen of the secondary neural tube. The process of canalization continues until the seventh week after conception.

5.3
Etiology of NTDs

Neural tube closure is a complex process determined by extrinsic and intrinsic factors. Consequently, NTDs have a multifactorial origin, involving both genetic and environmental factors as indicated in Table 1. Epidemiological studies reveal striking variations in prevalence as a function of geographical location, sex, ethnic groups, race, season of the year, maternal age and nutritional status, social class, and history of affected siblings.

5.3.1
Folate/Homocysteine Metabolism and NTDs

5.3.1.1
First Evidence of Primary Prevention of NTDs by Folic Acid: Recurrence and Occurrence Studies

Forty years ago early studies on pregnancy outcomes demonstrated a possible link between altered folate status and embryonic developmental defects [22]. In 1976, Smithells and colleagues [41], reported low serum levels of micronutrients, including folates, in mothers of children with NTDs. In a subsequent non-randomized intervention study in women who had previously had a fetus with NTD, they demonstrated an 86% lower risk of recurrence (i.e., the chance that a disease present in a family will recur in that family) of NTD associated with periconceptional multivitamin consumption containing 360 μg of folic acid [42]. Further studies led the British Medical Research Council to perform a multicenter intervention trial that showed that periconceptional folate supplementation could reduce the recurrence of NTDs [28]. The prevention of the occurrence (i.e., the chance that a disease will present for the first time in a family) of NTDs was later demonstrated in the large randomized-controlled study in Hungary [9]. More recently, a community-based intervention study documented the effectiveness of a daily dose of 400 μg of folic acid in preventing NTDs in China (Table 2) [1].

The findings of the British and Hungarian trials generated much research on folate metabolism in an effort to identify the genetic and biochemical bases of NTDs. Further observations that some mothers of NTD offspring had increased levels of homocysteine (Hcy) led the scientific community to focus on the homocysteine/folate metabolic pathway, which involves several enzymes and cofactors, as represented in Fig. 3.

5.3.1.2
Genetic Risk Factors

The molecular variants of genes of the homocysteine/folate pathway were tested in a high number of epidemiological studies aimed at establishing an association between genetic determinants of homocysteine and NTDs. Unfortunately, the methodologies applied to these studies were often different, wide variations of polymorphisms frequencies were found [51], and discordant results in different populations were obtained. Nonetheless, a common mutation in the methylenetetrahydrofolate reductase gene (MTHFR), the C677T transition, is now regarded to as a consolidated and independent risk factor for NTDs both in the mother and the fetus. In fact, a metanalysis of several studies performed worldwide on the MTHFR variant found that both the homozygous and the heterozygous mutated genotypes were associated with increased risk of NTD [2]. Besides the MTHFR C677T, other variants of genes involved in the homocysteine/folate metabolism have been associated with an increased risk of NTDs, namely MTHFR A1298C in combination with MTHFR C677T in the fetus [48], maternal and fetal methionine synthase reductase (MTRR) A66G [52], maternal and fetal reduced folate carrier 1 (RFC1) A80G [13], and the maternal trifunctional enzyme methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase/formyltetrahydrofolate synthase (MTHFD) R653Q [5].

Table 1. Recognized causes of neural tube defects. *MTHFR* methylenetetrahydrofolate reductase, *CBS* cystathionine-beta synthase, *MTRR* methionine synthase reductase, *RFC1* reduced folate carrier 1, *MTHFD* methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase/formyltetrahydrofolate synthase

Causes	
Syndromes	There are 103 recognized syndromes with spinal neural tube defects or anencephaly, such as chromosomal abnormalities, autosomal recessive Meckel's syndrome, single gene mutations (including homeobox genes)
Genetic risk factors	MTHFR C677T MTHFR C677T + A1298C MTHFR C677T + CBS 844ins68 MTRR A66G RFC1 A80G MTHFD G1958A
Environmental risk factors	Folic acid deficiency Mild hyperhomocysteinaemia Vitamin-B12 deficiency Diabetes Valproic acid Fever in early pregnancy Obesity Alcohol consumption Low socioeconomic status

Table 2. Risk reduction of neural tube defect recurrence and occurrence by folic acid (*FA*) supplementation or fortification. *MV* multivitamins

		References	Design	Intervention	Outcome (% reduction)
Supplementation	Recurrence	[25]	Randomized clinical trial	FA 4 mg	60
		[28]	Randomized clinical trial	FA 4 mg	72
		[7]	Randomized clinical trial	MV, FA 4 mg	60
		[42]	Cohort study	MV, FA 0.38 mg	86
		[49]	Cohort study	FA 5 mg	100
	Occurrence	[10]	Randomized clinical trial	MV, FA 0.8 mg	40 – 100
		[1]	Community-based intervention trial	FA 0.4 mg	40 – 80
		[50]	Case-control study	FA 0.4 mg	60
		[39]	Case-control study	MV, FA 0.4–0.9 mg	5 – 55
Fortification	Occurrence	[27]	Population based; intervention trial	FA 1.4 mg/kg flour	23
		[33]	Population based; intervention trial	FA 1.5 mg/kg flour	56
		[6]	Population based; intervention trial	FA 2.2 mg/kg flour	37

5.3.1.3
Metabolic Risk Factors

Folic Acid and Folates

Folic acid is a water-soluble B vitamin and is an essential nutrient since its de novo synthesis is absent in mammals. The term refers to the synthetic and rapidly absorbed form present in multivitamins or fortified foods. The natural form is referred to as folate, consists of 5-methyltetrahydrofolate (5-MeTHF) and 10-formyl-tetrahydrofolate (10-formylTHF) and is contained in a variety of fruits and vegetables such as green leafy vegetables, potatoes, oranges, and beans, even though a considerable amount of folate can be destroyed in cooking and storage.

The generic term folates indicates both the natural and the synthetic form.

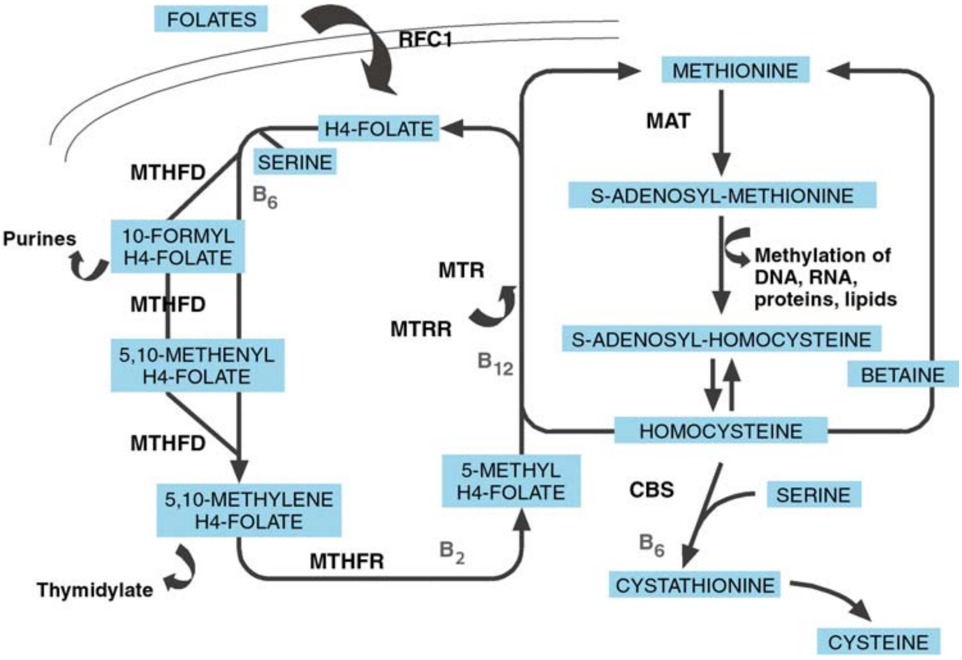
Folates have a crucial role in several interconnected metabolic cycles such as thymidilate and purine biosynthesis, serine and glycine interconversion, histidine and formate metabolism, methionine synthesis via homocysteine remethylation, and the synthesis of S-adenosyl-methionine, the most important methyl-donor in many methylation reactions of DNA, RNA, and proteins (Fig. 3). Folates are absorbed and transported across mammalian cell membranes by a carrier-mediated mechanism through the reduced folate carrier, by a receptor mediated uptake through a family of four folate receptors, or by passive diffusion.

In humans, reduced folate levels in maternal serum are associated with an increased risk of NTDs [24]; however, it does not appear that folic acid supplements act simply to correct dietary folate deficiency, since folate levels in NTD pregnancies, though located in the low part of the control range, are generally associated with a normal pregnancy outcome [47]. In mice, a folate-deficient diet is not sufficient to cause NTD. Nevertheless, in a mouse model of NTD, the knockout mouse for the folate-binding protein 1 (folbp1) [34], which displays severe and lethal morphogenetic abnormalities including small neural crest aggregation and delayed neural tube closure, maternal supplementation with folinic acid (N5-formyl-tetrahydrofolate) rescues embryonic lethality and leads to NTD only in 20% of cases: this suggests that NTDs in 80% of mice have been prevented by folinic acid administration. Genes that appear to be regulated by folates include transcription factors, G-proteins, growth factors, methyltransferases, and genes related to cell proliferation [43]. Other genetic models of folate-preventable NTDs involve knockout mice for transcriptional regulators. The three main folate-sensitive NTD mice strains, named Cart1, Cited2, and Splotch, display an excessive apoptosis in the developing neural tube. In all these examples, the prevention by folic acid may be due to a stimulation of proliferation that overcomes the excessive cell death. The experimental evidence from these models also suggest that folic acid administration has a true primary preventive effect, since the decline of NTDs is not due to increased loss of affected pregnancies but to an increased proportion of mutated embryos without NTD. On the bases of these observations, a potential mechanism for the protective effect of folic acid is stimulation of proliferation through provision of nucleotides for DNA synthesis. Alternative mechanisms that have been proposed are based on the identification of elevated maternal plasma levels of Hcy or reduced levels of vitamin B12, the cofactor of methionine synthase [24, 44]. The protective mechanism proposed is that folic acid supplementation results in provision of 5-methyl-THF that provides methyl groups for conversion of Hcy to methionine, thus enhancing the activity of methyltransferase or reducing potentially teratogenic levels of Hcy.

Homocysteine

Mild hyperhomocysteinemia has been detected in mothers of NTD-affected children and in maternal plasma and amniotic fluid in NTD pregnancies [30]. Elevated Hcy is often looked upon as being an indirect consequence of faulty folate metabolism, although more recent studies show that Hcy may act directly as a teratogen. In fact, Hcy is at the crossroads of protein and DNA metabolism, can chemically modify proteins directly and generate free radicals. A study on avian embryos pointed to a direct teratogenic effect of maternal hyperhomocysteinemia on neural tube closure and heart developmental anomalies, rescued by supplementation with folic acid [38]; however, the teratogenic dose

Fig. 3. The homocysteine and folates metabolic pathway



of Hcy was shown to raise serum homocysteine to over 150 nmol/ml, well above the normal level of 10 nmol/ml and even much higher than those defined as moderate hyperhomocysteinemia in the humans. A subsequent study demonstrated a teratogenic effect of Hcy on the neurulation sequence in avian embryos at lower doses [15], but this effect has not been replicated in mammals. In fact, three independent studies failed to demonstrate an increase of NTD embryos in rats and mice models treated with increasing Hcy dosage [17, 21, 45]. In conclusion, it is still unclear if elevated Hcy is a cause of human NTD or, more likely, a marker of abnormal folate or methionine metabolism. Indeed, low methionine levels seem to cause abnormal neurulation and NTDs in rats and methionine supplementation can prevent NTDs in several mouse models [8, 18].

Vitamin B12

Vitamin B12 has a crucial role in the remethylation of Hcy to methionine, being the cofactor of the methionine synthase enzyme. It represents a well-established determinant of Hcy levels and it has been shown to be a risk factor for NTD in mothers with low vitamin B12 serum concentrations and in a subset of NTD children, independently from the genotype [20, 47]. Also, low vitamin B12 levels in both NTD mothers and children interact with the mutated MTRR A66G polymorphism, increasing the risk by nearly five times and 2.5 times, respectively, and providing additional evidence of the multifactorial origin of NTD [52].

5.3.1.4
Gene–Gene and Gene–Environment Interactions

Besides the role of single genetic and metabolic factors in NTDs, a growing wealth of studies indicates the importance of gene–gene and gene–environmental interactions in the etiology of NTD; thus, a multi-locus rather than a single locus analysis would be more efficient to gain an accurate assessment of genetic susceptibility to NTDs [37]. This means that more than one gene is likely to participate in determining the genetic background of NTDs, though the MTHFR 677TT genotype remains as the strongest factor. The literature already provides examples of the importance of gene–gene and gene–environment interactions. A common mutation (844ins68) in the cystathionine-beta-synthase gene is not a risk factor for NTD by itself, but increases the risk of NTD of nearly four times when it is associated to the MTHFR C677TT genotype [12]. The homozygosity for the MTHFR A1298C common mutation results in decreased MTHFR activity but is not clearly associated to increased risk of NTDs [48]; however, the joint effect of the C677T and A1298C mutation causes a 2.8-fold increased risk of NTDs. In both cases, the NTD risk associated to the combined genotypes is higher than the risk attributable to the two alleles analyzed individually. Furthermore, the above-mentioned MTRR A66G polymorphism is a genetic risk factor for NTDs, in particular when associated to vitamin B12 deficiency [52]. Finally, interactions between maternal and fetal genotypes might be additional risk factor for NTDs. Indeed, it has been shown a six- to sevenfold increased risk of NTDs, if both the mother and the child are homozygous for the MTHFR C677T polymorphism [46].

5.4
Preventive Strategies of NTDs

5.4.1
Folate-Preventable NTDs: Primary Prevention by Folic Acid

A large number of studies have stated the importance of folate supplementation in the prevention of congenital defects and defined three main strategies for folate status improvement: food fortification; folic acid supplementation for all women likely to become pregnant; and general dietary education. Each strategy presents advantages and challenges that are discussed below. Increased consumption of foods with high levels of natural folates was proved ineffective in raising folate status due to the incomplete bioavailability.

5.4.1.1
Fortification

A food fortification strategy has been adopted by several nations including U.S., Canada, Chile, and Salvador. Food fortification rather than supplementation in pregnancies was deemed necessary because of a perceived failure of public health efforts to influence persons at risk since neural tube closure occurs during the first 4 weeks of pregnancy when women are still unaware of their status. Also, fortification provides folates to almost all women, is inexpensive, and has proved to increase blood folate levels.

In 1998, the U.S. Food and Drug Administration mandated fortification of cereal grain products with folic acid to prevent NTDs by increasing women's daily intake. Since fortification, the Centers for Disease Control and Prevention (CDC) have found a 23% reduction of NTD rates [27]. After mandatory folate fortification, also significant increases in plasma folate and reductions in total plasma Hcy were observed in the Framingham study offspring [23]. Moreover, folate fortification might reduce the risk for other diseases associated with low folate status and/or mild hyperhomocysteinemia, e.g., cardiovascular disease.

Because of concerns that folate fortification may mask symptoms of vitamin-B12 deficiency, primarily in the elderly population, the level of fortification chosen by the FDA requires an average 100 µg additional folic acid daily. Initial estimates by the FDA anticipated an increase in folate intake by adults between 70 and 130 µg/die, but many post-fortification studies assessed an increase in folate intake about twice the previsions [26, 35, 36]. This obligate folate intake should be summed to the intake of dietary folates and voluntary supplementation with folic acid or multivitamins. In this scenario, a higher proportion of the population than that expected from the FDA guidelines would consume more than 1 mg/die of folic acid, the limit chosen as safe. This can cause the following potential problems:

1. Although small doses of oral folic acid are efficiently metabolized to 5-methyl-THF before entering the portal blood, intakes >200 µg appear to overload this metabolic capacity, leading to unmetabolized folic acid in plasma, whose effects are not yet known.
2. High folate intakes may prevent the accompanying folate deficiency and mask the underlying cobalamin deficiency, delaying the diagnosis of megaloblastic anemia.
3. Folates can eventually interfere with antifolates drug therapies. At the time of the FDA decision, only few data were available, and this crucial point needs further investigation.
4. Fortification may cause different intakes depending of the sex and age subgroups according to the quality and quantity of fortified foods consumed. The study by Lewis et al. [26] estimated that 15–25% of children aged 1–8 years had higher folates intake than recommended, while 68–87% of females of childbearing age had intakes below 400 µg/die.

This study shows the need to improve folate intake in targeted subgroups, including women of childbearing age, while not putting other population subgroups at risk of excessive intakes. No European country has started folate fortification yet. The United Kingdom's Food Standards Agency Board and the Dutch Health Council decided against this mandatory fortification. As a consequence, in Europe, as well as in other countries without folate fortification, reproductive-age women need periconceptional folate supplementation to reduce the risk of NTDs in their offspring.

5.4.1.2
Supplementation

After the release of the two randomized studies, the U.S. Public Health Service recommended in 1992 that women capable of becoming pregnant consume 400 µg of folic acid per day. Because half of pregnancies are unplanned, and because the neural tube develops before most women realize that they are pregnant, it was recommended that women consume this amount of folic acid routinely. Whether hyperhomocysteinemia and/or folate deficiency underlie the molecular pathogenesis of NTDs, programs of folate supplementation or fortification have produced a reduction of both occurrence and recurrence of NTDs. In fact, voluntary periconceptional supplementation of folic acid in reproductive-age women reduces the occurrence of neural tube defects by 50–70% [9, 28]. Also, it is now clear that folic acid supplementation reduces the risk of other congenital anomalies, such as orofacial clefts, heart defects, limb deficiencies, and urinary tract defects [3]. Unfortunately, European women in the childbearing age range have dietary folate intakes below the optimal level of 400 µg/day [11]. Since folate supplementation should take place between 4 weeks before and up to 12 weeks after conception, this preventive measure can seldom be applied in the right terms. The European policy may, therefore, appear weak and losing. Indeed, a recent retrospective cohort study aimed at evaluating the effectiveness of policies and recommendations on folic acid using data from 13 birth-defect registries found no improvement in the trends of incidence of NTDs [4]. Some authors claim that a reasonable strategy would be to integrate fortification with a fuller implementation of the recommendations on folic acid, in order to overcome the economic and educational disparities induced by the supplementation strategy. Strategies to make effective the policies and the recommendations on folic acid aimed at reducing the occurrence of NTDs should include intensive educational efforts of specific population subgroups (i.e., women of childbearing age) by public health providers, physicians, social services, and the provision of free folic acid tablets to subgroups at risk. Indeed, an intensive Public Health policy and the high proportion of planned pregnancies have been the crucial factors in the highly effective campaign in China.

5.4.2
Folate-Resistant NTDs: Other Possible Preventive Strategies

Clinical trials demonstrate that up to 70% of NTDs can be prevented by folic acid supplementation in early pregnancy, whereas the remaining NTDs are resistant to folates. Data regarding the efficacy of food fortification suggest that there has been a decline in the incidence of NTDs in the U.S. post-fortification, whereas it has been estimated that 0.5–0.7 per 1000 pregnancies cannot be prevented by the current therapeutic strategies [29]. Several important lines of evidence point to a second vitamin, myoinositol, that may have a potential role in the normal closure of the neural tube. In fact, myoinositol is important in intracellular signaling pathways through the stimulation of the protein kinase-C activity and the upregulation of the expression of retinoic acid receptor beta in the caudal portion of the embryonic hindgut, reducing the delay in closure of the posterior neuropore.

Groenen et al. [19], in a case-control study of mothers of infants with NTDs, observed a nearly threefold increased NTD risk associated with low myoinositol levels measured in post-partum serum. Also, murine studies indicate that supplementation with myoinositol reduces the frequency of spina bifida in curly tail mice, a genetic model of folate-resistant NTDs [16]. Finally, there is evidence of increased NTD rates associated to conditions with abnormal glucose control, such as diabetes, gestational diabetes, and obesity. It is known that glucose inhibits the absorption of myoinositol, resulting in its depletion. A very recent case-control study [40], on a large sample size of NTD mothers and controls, could not confirm the previous results; however, the study estimated the inositol intake through a food frequency questionnaire that may result in inaccuracies in the estimation of myoinositol dietary content; also, the authors could not evaluate the de novo synthesis of myoinositol that occurs in human tissues. Nevertheless, myoinositol seems to be a promising vitamin to reduce an additional portion of NTDs, even if stronger evidence coming from large randomized clinical trials are warranted to lead to new public health strategies.

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Developmental Anomalies Responsible for Neurogenic Bladder Dysfunction

6

Jean Louis Lemelle · Oliver Klein

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6.1
Introduction

Many conditions affect vesicourethral function. In most cases, neurogenic bladder dysfunction is seen in conjunction with other obvious neurological conditions or malformations. Neurogenic bladder dysfunction is rare, as revealed by multiple clinical examinations for functional or maturational voiding disorders unrelated to neurogenic defect. Sometimes, however, isolated vesicosphincteric dysfunction may permit detection of an unknown medullary lesion. Most neuropathic disorders are linked to abnormal spinal column development. Myelodysplasia encompasses a wide range of developmental anomalies such as spinal dysraphism (including myelomeningocele, spinal lipoma, dermoid cysts, and dermoid sinus), which results from defects in neural tube closure.

6.2
Normal Development of the Nervous System

6.2.1
Gastrulation

Formation of the spinal cord and vertebrae begins around day 18 of gestation. After fertilization and the first rounds of cell division, the human embryo comprises a spherical blastula containing a peripheral ring of trophoblast cells destined to develop into the placenta. The inner cell mass will form the embryo. By the end of the first week of gestation, the inner cell mass becomes suspended within a sphere and comprises two layers: the epiblast and the hypoblast. The epiblast lies dorsally to the amniotic sac, whereas the hypoblast, situated ventrally, lies adjacent to the yolk sac or umbilical vesicle. During the second week, a rostrocaudal axis develops. Epiblast cells in the caudal region of the embryo migrate toward the midline to form the primitive streak in the caudal embryonic midline. At the cranial end of the primitive streak lies the primitive knot or Hensen's node. Cells within the primitive streak and Hensen's node invaginate beneath the epiblast in a process known as gastrulation. The earliest invaginating epiblast cells displace the underlying hypoblast cells and become the embryonic endoderm. Epiblast cells which invaginate later form the embryonic mesoderm. The epiblast cells that remain form the ectoderm. The endoderm give rise to the enteric and respiratory endothelium, the mesoderm give rise to the somites and mesenchyme, and the ectoderm give rise to the surface ectoderm and neuroepithelium [18]. The primitive streak, which initially is limited to the caudal pole of the embryo, elongates during the first part of gastrulation until it encompasses the caudal half of the embryo; thereafter, the primitive streak regresses back toward the caudal end of the embryo. During this process, cells within Hensen's node form the midline notochordal process between the overlying neuroepithelium and the underlying endoderm. The notochordal process is initially rod shaped and has a central lumen, the notochordal canal, which is continuous with the amniotic cavity through the primitive pit. The notochordal process eventually fuses with the underlying endoderm to form the notochordal plate. The notochordal canal lasts approximately 3 days; thereafter, the notochordal plate detaches from the endoderm, and the primitive neurenteric canal closes. Abnormal development of the midline axis during gastrulation may account for some myelomeningoceles, split cord malformations, and a number of other complex dysraphic malformations [11].

6.2.2
Primary Neurulation

Primary neurulation, which occurs between days 18 and 26 of gestation, includes the development of a midline neural groove and the dorsal elevation of the adjacent neural folds (Fig. 1). Eventually, elevation and medial convergence of the neural folds bring the neuroectoderm together in the midline to form the neural tube. Separation of the neural tube from the overlying cutaneous ectoderm completes the process. Mesenchymal tissues are later interposed between the neural tube and cutaneous ectoderm to form the paraspinous muscle and dorsal vertebra arch. There are currently two models of human neural tube closure. The traditional model proposes that neural tube closure begins in the midcervical region and propagates in both cranial and caudal directions. An alternate model suggests that multiple areas of the neural tube close simultaneously, and that closure of the remaining neural tubes involves intercalation between these multiple points.

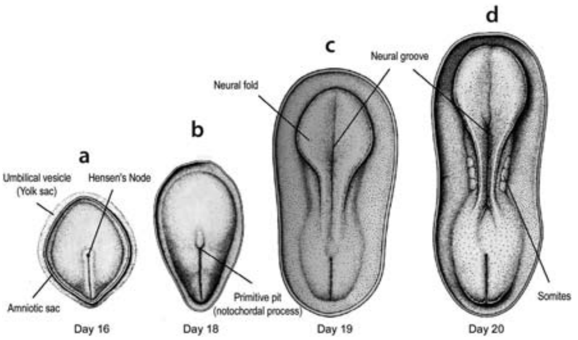

Fig. 1. **a,b** Normal human gastrulation: prospective notochordal cells in the canal margin of Hensen's node ingress through the primitive pit to become the notochordal process. **c,d** Primary neurulation: the midline neural groove is formed above the notochordal tube and the neural folds are elevated to form the neural tube.

The last areas of the neural tube to close are the cranial and caudal neuropores. The cranial neuropore closes around gestational day 24. The caudal neuropore closes around day 26 at the level of the second sacral spinal cord segment. More caudal regions of the neural tube (the spinal cord caudal to the S2 segment and the filum terminale) are formed thereafter through secondary neurulation.

6.2.3
Secondary Neurulation

During secondary neurulation, the caudal neural tube develops from the caudal cell mass, a pluripotent group of cells representing the regressing Hensen's node at the caudal embryonic pole which additionally gives rise to the caudal mesenchymal precursors of the sacrum and coccys. The secondary neural tube eventually fuses with the neural tube formed by primary neurulation. The process of human secondary neurulation is a matter of ongoing discussion. The process has been more precisely observed in avian and mouse embryos, with specific differences according to species particularly as pertaining to the role of the caudal cell mass and primary neurulation.

6.2.4
Spinal Occlusion

During neural tube closure, the lateral walls of the developing spinal cord become transiently opposed and obliterate the lumen of the developing spinal cord [10], a process referred to as spinal occlusion. In humans, spina occlusion begins with anterior neuropore closure at gestational day 24 and continues throughout the period of caudal neuropore closure, ending around gestational day 32. After the closure of the cranial neuropore, the cranial neural tube lumen effectively becomes a closed fluid-filled space, and expands rapidly due to the growth of the neural tube and, subsequently, to the dilatation of the ventricular system. This suggests that spinal occlusion plays a critical role in embryonic development of the brain and ventricular system. If, during the phase of rapid brain enlargement, the cranial lumen is vented externally, then brain expansion is significantly reduced and the brain develops abnormally. Similarly, failure to spinal occlusion process in embryos with myelomeningocele may produce cranial and mesenchymal abnormalities collectively referred to as the Chiari malformation [20].

6.2.5
Ascent of the Conus Medullaris

By approximately gestational day 45, the caudal end of the neural tube extends to the coccygeal spina level; thereafter, the caudal end of the neural tube begins to ascend to progressively more cranial spina levels. This process is referred to as the ascent of the conus medullaris (Fig. 2). Ascent of the conus involves two mechanisms. Between gestational days 45 and 54, ascent involves a series of morphogenetic changes, called retrogressive differentiation, in which the caudal neural tube loses diameter, fails to develop a distinct mantle zone, exhibits only a thin, rudimentary, marginal zone, and generally appears less well developed than it did at earlier embryonic stages. The caudal end of the neural tube is more slender and fibrous and becomes the filum terminale. Beyond gestational day 54, ascent results in the differential growth of the spinal cord and spinal column. Ascent is initially more rapid between the eighth and twenty-fifth weeks of gestation, and tapers off near term [1]. Between 1 and 2 months after birth, the conus medullaris normally lies opposite or cranial to the L1–L2 disk space. A conus that lies below this level suggests spinal cord tethering.

6.2.6
Myelomeningocele

Myelomeningocele is a form of spina bifida in which a focal segment of spinal cord appears as a flat plate of neural tissue that is exposed to view, protruding from the midline of an infant's back (Fig. 3).

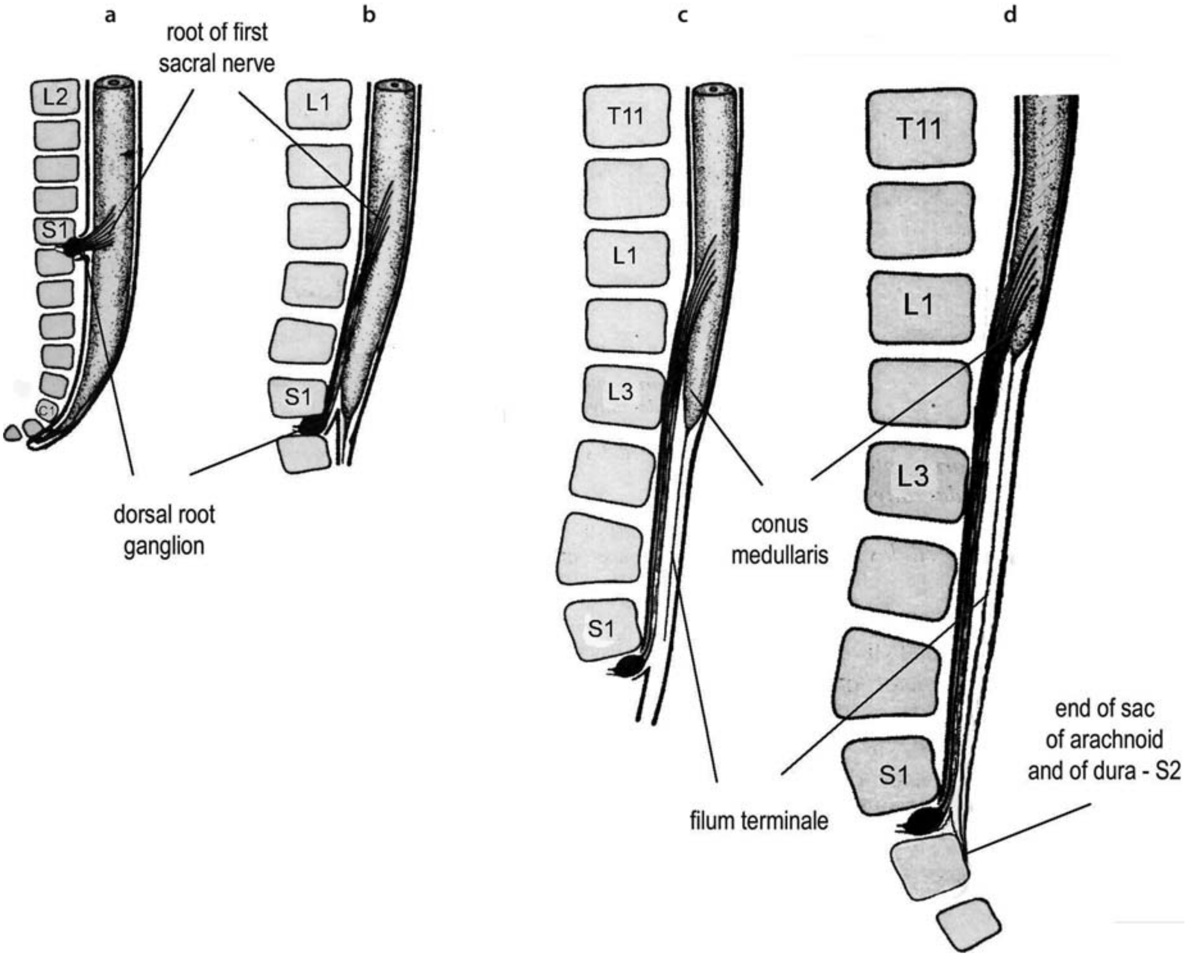

Fig. 2. Progressive ascent of the conus medullaris from embryogenesis to the normal anatomic status. **a** At 8 weeks of gestation. **b** At 24 weeks of gestation. **c** Newborn. **d** Childhood

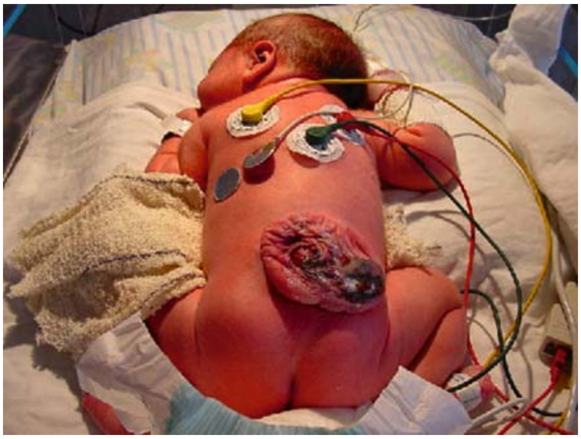

Fig. 3. Large lumbar myelomeningocele in a newborn infant

6.2.7
Embryopathology of Myelomeningocele

A localized failure of neural tube closure results in a neural tube defect. Should this failure involve the cranial neural tube, it will result in anencephaly, whereas involvement of the caudal end will result in myelomeningocele. There are generally two theories regarding the origin of neural tube defects. The nonclosure theory, elaborated in 1886 by von Recklinghausen, attributes neural tube defects to a primary failure of neural tube closure. The overdistension theory, introduced in 1729 by Morgagni and more recently popularized by Gardner [14], attributes neural tube defects to the overdistension and rupture of a previously closed neural tube. The nonclosure theory, consistent both with observations in early human embryos and with most animal models of neural tube defects, has gained almost universal acceptance, whereas the overdistension theory has largely been discarded. Nevertheless, overdistension should not be excluded as a cause of some neural tube defects, particularly those produced by retinoic acid [3].

A number of clinicians have attempted to distinguish myelomeningocele from myeloschisis, implying that these two lesions have different embryonic origins. Accordingly, myelomeningocele has traditionally referred to an open neural tube defect with a fluid-filled sac, whereas myeloschisis refers to a larger and flatter neural tube defect having no evidence of a central canal or investing meninges. This classification, however, is arbitrary and imprecise, because in both malformations a portion of the neural tube has failed to close, the exposed neural tube (the placode) and its central canal are open dorsally, and the lateral edges of the neural folds are still attached to the adjacent cutaneous ectoderm. Both lesions, therefore, most likely arise through a localized failure of neurulation. Because the peripheral edges of the placode remain attached to the cutaneous ectoderm, cerebrospinal fluid (CSF) accumulates in the developing subarachnoid space beneath the placode. The extent to which the CSF accumulates ventrally and displaces the placode dorsally determines the type of malformation: accumulation of CSF beneath the placode elevates the neural placode to the top of a fluid-filled sac and produces a myelomeningocele, whereas venting of CSF allows the placode to lie flat and produces a myeloschisis. As a consequence, McLone and Dias [18] have suggested that the term myeloschisis be discarded and that all such lesions be referred to as myelomeningoceles.

Myelomeningocele may result from a disruption involving any of the embryonic processes described previously. A number of teratogenic agents which produce neural tube defects during specific phases of the neurulation sequence have been identified. In experimentally treated embryos, neural tube defects have been observed when the following agents have been added: cytochalasins and vinblastine disrupt actin microfilaments; calcium channel blocking agents interfere with calcium-mediated microfilament contraction; phospholipase C and concanavalin A disrupt cell-surface glycoproteins; and n-cadherin messenger RNA results in misexpression of n-cadherin cell surface adhesion molecules [23]. In certain animal models, other agents, such as retinoic acid (vitamin A), hydroxyurea, and mitomycin C, may produce neural tube defects by interfering with the timing of neuroepithelial development relative to the development of adjacent non-neural tissues.

6.2.8
Clinical Epidemiology of Myelomeningocele

Many demographic studies of myelomeningocele have included a number of congenital anomalies under the heading of neural tube defect. Myelomeningocele and anencephaly, both neurulation disorders, and encephaloceles, representing postneurulation disorders, have often been included in the same grouping [4]. Even congenital hydrocephalus stemming from a variety of causes unrelated to myelomeningocele has been included in some studies. Many epidemiological studies are therefore flawed by including these other disorders in the analysis.

Moreover, there is growing evidence that myelomeningoceles may be etiologically and embryologically heterogeneous [4, 11]. For example, some myelomeningoceles may arise embryologically through a primary disorder of neuroepithelial development during gastrulation which later disrupts neurulation secondarily, whereas others may represent a direct neurulation defect. Clinically, at least three different patterns of myelomeningocele have been described. The first type occurs among Celtic descendants and is characterized by high-level lesions with high sensorimotor levels and frequent mental retardation. The second type occurs among Spanish and Arabian descendants and is characterized by unusually good sensorimotor function and minimal mental retardation despite high-level lesions and marked hydrocephalus. The third type occurs among Sikhs living in western Canada and is characterized by high-level lesions and relatively preserved sensorimotor function [25]. Myelomeningocele currently occurs with an overall frequency of approximately 0.7–0.8 per 1000 live births, but with marked variations from region to region. For example, the incidence in the UK varies from 0.7 to 2.5 per 1000 live births, but that in Ireland is as high as 5 per 1000 live births. In the U.S. the frequency is between 0.41 and 1.43 per 1000 live births and is lower among African-Americans than Caucasians. Native Africans have a very low incidence of 0.1 per 1000 live births [25]. The incidence of myelomeningocele worldwide has declined significantly over the past decade; in the U.S., for example, the rate dropped from 0.6 to 0.3 per 1000 live births between 1984 and 1992 [6]. This decline has partially been ascribed to improved maternal nutrition and periconceptional vitamin supplementation, as well as to wider availability of prenatal diagnostic tests (with a corresponding increase in the number of elective terminations); however, these factors account for only a portion of the decline, and other reasons are as yet unknown.

The recurrence risk for parents with one previously affected child rises to about 1–2% for subsequent pregnancies [4, 25]. For those having two affected offspring, the rate may be as high as 10%. For a parent with a myelomeningocele, the risk of bearing a child with a myelomeningocele is about 3%. Although myelomeningoceles most often occur as an isolated malformation, there are occasions in which they are found as part of a defined genetic syndrome. Associations between myelomeningocele and trisomy 13 and 18, for example, are common among abortuses but are rare among live births, suggesting early fetal death [16].

6.2.9
Prenatal Diagnosis

Technological advances permit the prenatal detection of myelomeningoceles and spinal dysraphism. Available methods include maternal serum alpha-fetoprotein (AFP) levels, amniotic AFP and acetylcholinesterase (AchE) levels, ultrasound, and, more recently, fetal magnetic resonance imaging (MRI). Elevated AFP levels successfully indicate an open neural tube defect (anencephaly and/or myelomeningocele) with a sensitivity of about 75%. A high maternal serum AFP level is not, however, specific to fetal neural tube defects. Other conditions, such as underestimated gestational age, multiple pregnancies, and other fetal disorders, such as omphaloceles, can produce similar increases; nor can it detect skin-covered spinal malformations such as myelocystoceles, some meningoceles, and disorders of secondary neurulation that occur in the presence of intact skin. Alpha-fetoprotein is an alpha-globulin that is synthesized by the fetal liver and excreted renally into the amniotic fluid. Since amniotic AFP levels vary with gestational age, levels must be compared with the normal median for the gestational age at the time of sampling. The AFP levels in the CSF are approximately 100 times greater than normal amniotic fluid AFP levels. Leakage of CSF through an open neural tube defect therefore results in a significant increase in amniotic AFP levels. Nevertheless, measurements of amniotic AFP are not foolproof: while the amniotic AFP concentration is raised in 97% of women carrying an affected fetus, there is no clear cut-off that absolutely separates normal from affected pregnancies. Moreover, the amniotic AFP level may be increased in a variety of other fetal conditions. For these reasons, both AFP and AChE are measured contemporaneously. Amniotic AchE measurements also reflect fetal neural tube defects and are, on average, more sensitive than amniotic AFP measurements.

False-positive increases of both AFP and AchE levels may occur with fetal blood contamination during sampling, fetal autolysis, or in cases of impending fetal death, and other significant fetal anomalies, including abdominal wall defects. Furthermore, as in the case of maternal serum AFP levels, neither amniotic AFP nor amniotic AchE levels will be elevated in the presence of skin-covered malformations. In the modern diagnosis of suspected fetal abnormalities, it is important to use a combination of diagnostic tools. Due to its accuracy, prenatal ultrasound is the most popular diagnostic tool for neural tube defects. The spinal placode can be visualized directly and/or associated vertebral anomalies may be apparent. Indirect signs of a myelomeningocele, such as the "banana" and "lemon" signs seen on cranial imaging, are highly predictive of myelomeningocele, even when the spinal anomaly cannot be identified directly. The "lemon sign" represents the concave inward appearance of the frontal bones, whereas the "banana sign" represents the elongated appearance of the cerebellum due to the Chiari malformation. These cranial signs may miss small caudal malformations lacking a Chiari malformation. If a neural tube defect is identified, other significant or lethal fetal anomalies should be sought, as these may be important in determining both the probability of survival and quality of life. Evaluation of prenatal diagnosis of neural tube defects by ultrasound examination in unselected populations across Europe was reported by Boyd et al. [2]. On the basis of Congenital Malformation Registers from 11 European countries, 542 cases of neural tube defect were diagnosed at delivery over a 30-month study.

The lesion was isolated in 84% of the cases (166 anencephaly, 252 spina bifida, 35 encephalocele). In cases with anencephaly, 96% were correctly identified prenatally (with a sensitivity of 98%). Of the prenatal diagnoses, 84% were made before 24 weeks of gestation. Of 252 cases of isolated spina bifida, 68% were correctly identified prenatally, 68% of which were detected before 24 weeks of gestation. The diagnosis was missed on scan in 60 cases and scanning was not used in 21 cases (sensitivity of 75%).

Accurate fetal imaging is essential to the practice of maternal-fetal medicine. While ultrasonography has been the traditional mainstay of fetal imaging, its ability to resolve critical features of central nervous system (CNS) anatomy remains limited. As interest in intrauterine therapy for myelomeningocele has increased, so has the need for more accurate, non-invasive imaging of the CNS. Fetal MRI promises to fill the gap left by ultrasound. Recent studies concluded that MRI is an effective, non-invasive means of assessing fetal CNS anatomy. Its ability to resolve posterior fossa anatomy is superior to that of ultrasonography. Inclusion of the fetal MRI into the standard diagnostic armamentarium will probably await the next major advance in speed and resolution. It is conceivable that, with further advances, MRI might supplant ultrasonography as the diagnostic tool of choice for evaluation of fetal anomalies including myelomeningocele [17].

6.2.10
Prenatal Counselling

As the prognosis of fetal malformation is valued considerably by parents, providing counselling requires accurate information on follow-up care of patients with myelomeningocele. Although personal experience, religious and cultural beliefs, and ethical principles may bias the parent's perspective, the clinician must refrain from making a decision for the parents since, after all, it is the parents who will care for the child. Although it is important to be as forthright and comprehensive as possible, one must avoid overwhelming the parents with too much information, as such a prognosis often results in parental shock and disbelief. Relevant information may therefore need to be imparted over several sessions.

Spina bifida is the most common malformation affecting the nervous system. In the absence of other fatal anomalies, almost all treated infants survive [19]. The first objective of treatment is to repair the placode in order to prevent infection and to protect the spinal chord. There is an 85–90% chance that the child will require further surgical treatment for progressive hydrocephalus, and shunt revision may also be necessary over the following years.

With respect to intellectual performance, approximately 75% of affected individuals have intelligence quotients above 80, and, in the absence of CNS infection, the presence of hydrocephalus does not substantially change this statistic. Nevertheless, learning disabilities are apparent in half of these children: verbal scores are typically higher than performance scores on standardized tests, and math, problem solving, and the sequencing of information tend to be particular weaknesses [12].

Ambulation depends on the level of the lesion and the extent of the sensorimotor deficit. A minor percentage of affected individuals cannot ambulate due to severe developmental delays, hypotonia, or both. Most preadolescent children are community ambulators, including 100% of those with low lumbar and sacral level lesions, and half of those with higher lesions. The rate of ambulation falls to about 50% during adolescence, as it becomes more energy efficient to use a wheelchair. Bony deformities of the lower extremities may require orthopedic correction or braces. The incidence of scoliosis depends on the spinal level but occurs in up to 85% of children with myelomeningocele and may require surgical intervention such as spinal cord tethering, cervicomedullary decompression for Chiari malformation, shunting of hydrosyringomyela, or spinal fusion.

Most school-aged children are socially continent through a combination of medications, Crédé maneuvers, and/or clean intermittent catheterization regimens. During adolescence, many require urological surgery to improve social continence, whereas intermittent catheterization will remain the basis of urological management. Most patients suffer chronic constipation and many require a regimen of laxatives and bowel enemas in order to achieve proper evacuation. Although insensate, the person with a myelomeningocele can sometimes attain reflex sexual functions, and people with myelomeningocele have become parents.

There is a noteworthy observation about cervical or cervicothoracic level myelomeningoceles, which are rare but which carry a very different prognosis [21]. Children with cervicothoracic myelomeningocele are fundamentally different from those having lumbosacral lesions. Cervical myelomeningoceles are typically closed lesions and are covered with intact skin or a thick membrane. The involved neural tissue is usually only a thin stalk which passes from the spinal canal to the sac through a tiny mesenchymal opening and which is attached to an intact underlying spinal cord. Underlying split cord malformation may be associated. Usually, cervical and upper thoracic myelomeningoceles have a low risk of voiding disorders and upper tract deterioration, unless other conditions, such as a congenital tethered cord, are present. Armed with the correct information, parents are in the best possible position to make intelligent decisions, for themselves, about the future of their child. Accordingly, to the risk of major sequella, parents may decide to terminate the pregnancy. In the Boyd et al. European study [2], prenatal diagnosis of spina bifida leads to a mean reduction in birth prevalence up to 49% (range 6–100%). Wide statistical variations were observed between centers: the rate of prenatal detection (33–100%), the rate of termination of pregnancy in prenatally diagnosed cases (17–100%), as well as the gestational age both at diagnosis and termination of pregnancy. These variations reflect differences both in policy and culture.

6.2.11
Initial Care of the Infant with Myelomeningocele

Initial postnatal management consists of stabilizing the infant, identifying any associated abnormalities, closing the myelomeningocele, and treating associated hydrocephalus, when present. The initial assessment of the newborn with a myelomeningocele should entail a close inspection of the spinal level and the size of the lesion, the redundancy and quality of the surrounding skin, and the presence of any associated kyphosis, which could affect the difficulty of repair. A modest-sized flat sacral lesion may look deceptively simple but is often difficult to repair because of problems in mobilizing the surrounding skin in the region of the sacrum and buttocks. In contrast, a large cystic thoracolumbar lesion which at first seems insurmountable can often be repaired without difficulty after widely mobilizing the skin. An asymmetrically positioned placode with a unilateral or asymmetric neurological deficit should suggest a hemimyelomingocele.

Sensorimotor level is determined by observing both spontaneous movements of the lower limbs as well as responses to sensory stimulation. In addition, characteristic positions of the lower limbs may suggest sensorimotor imbalances. For example, a characteristic knee extension posture in an infant with an L3 or L4 sensorimotor level may suggest an imbalance between the strong quadriceps (L2–L4) and weak hamstring (L5, S1) muscles, whereas a dorsiflexion deformity of the foot in a child with an L5 sensorimotor level suggests an imbalance between tibialis anterior (L4) and gastrocnemius/soleus (S1) muscles.

About 15% of newborns with myelomeningocele have obvious hydrocephalus at birth. The remainder vent CSF through the open placode and develop overt hydrocephalus only after the initial repair. A large head, bulging fontanelle, split sutures, and limitation of upward-gazing or "sunsetting" eyes suggest hydrocephalus. Routine ultrasonography or computed tomography (CT) is usually performed immediately after birth, both to assess ventricular size and to exclude other major developmental abnormalities of the brain. A careful assessment of lower cranial nerve and brainstem function should also be made. Poor feeding or nasal regurgitation, a weak or high-pitched cry, stridor or vocal cord palsies, central apnea and hypotonia, poor head control, or weak upper extremities may imply significant brainstem compression from the Chiari malformation and portend a worse prognosis.

The placode should be protected after birth since it often contains at least partially functioning neural tissue. Spontaneous movements of muscles innervated by the placode are apparent in many infants, and stimulation of these spinal roots during surgery can evoke muscle movements. Moreover, somatosensory evoked potentials within the placode can be elicited after peripheral nerve stimulation in some infants, and cortical evoked responses can be elicited following electrical stimulation of the placode. More than one-third of infants have sensorimotor functions after closure, which were not initially observed at birth. Finally, even if descending cortical input is absent, the placode can still subserve localized spinal reflexes, which are important in bladder and bowel function. The malformation is initially covered with gauze dressings soaked in sterile saline solution. Iodine-containing solutions, such as povidone–iodine, can injure live tissues and should be avoided. Plastic wrap may be placed atop the gauze to keep the dressings moist. Systemic antibiotics (a combination of ampicillin and an aminoglycoside) are usually provided for the first three postnatal days to protect against both CSF and urinary tract infections.

In order to avoid neurological deterioration and meningitis, the placode should be closed within the first 48 h after birth. During closure, it is helpful to conceptualize the placode in its embryonic state, as a neural plate that has failed to neurulate, and neural folds that are therefore still attached to the surrounding cutaneous ectoderm. Should any associated spinal cord anomalies be present, they should be dealt with during the closure. Split cord malformations are present in as many as 40% of infants with myelomeningocele; most are located within or immediately adjacent to the placode. These malformations may be associated with midline tethering, bony spurs, or fibrous bands which should be excised. The hemimyelomeningocele is a special type of split cord malformation in which one of the two hemicords is not neurulated, ends in an eccentrically placed open placode, and is associated with an ipsilateral neurological deficit, whereas the contralateral neurulated hemicord remains within the spinal canal and subserves the neurologically intact limb.

Caudal to the placode, an intact filum terminale may be present and should be sectioned, as it may provide a source of persistent tethering. In rare cases, other spinal anomalies may be associated with a myelomeningocele, including spinal lipoma, dermoids, neurenteric cysts, or even bowel loops – the split notochord syndrome – or combined spina bifida. Such anomalies should also be repaired at the time of closure in order to prevent subsequent tethering.

6.2.12
Initial Treatment of Hydrocephalus

Several pathophysiological mechanisms may act alone or in concert to cause hydrocephalous in patients with myelomeningocele. Aqueductal occlusion, fourth ventricular outlet obstruction, obliteration of the subarachnoid space by the crowded posterior fossa contents, and obstruction at the level of the tentorial hiatus have all been implicated. All of these mechanisms potentially have a common origin in the Chiari malformation, which leaves the posterior fossa contents tightly compacted in a small posterior fossa. This compaction impedes the normal flow of CSF from the third to the fourth ventricule through the cerebral aqueduct, from the fourth ventricule to the posterior fossa subarachnoid space through the ventricular outlets, and from the posterior fossa subarachnoid space through the incisura to the cerebral convexities, with resulting hydrocephalus. Frequently, hydrocephalus is mild or absent at birth and becomes evident only days or weeks after the myelomeningocele is closed. This delayed hydrocephalus is more frequently the result of occlusion within the subarachnoid space, usually in the posterior fossa or the tentorial hiatus. Clinical examinations are supplemented with serial ultrasonographic or CT measurements of ventricular size. Progressive enlargement on subsequent examinations suggests developing hydrocephalus.

Hydrocephalus is most commonly treated with ventriculoperitoneal shunting. The ideal location for the proximal shunt catheter is a matter of debate, with advocates of both frontal and occipital shunting.

6.2.13
Urological Prognosis

During childhood, patients with myelomeningocele may compromise their upper and lower urinary tract and, consequently, kidney function. A small percentage of newborns with myelomeningocele have abnormal urinary tracts. Anomalies result from abnormal lower urinary tract function in the form of outlet obstruction with secondary vesicoureteric reflux and ureterohydronephrosis. It has become increasingly important to assess urodynamic characteristics of detrusor and urethral sphincter. Combining bladder contractility and external sphincter activity results in several categories of lower urinary tract categories: synergic or dyssynergic; with or without detrusor hypertonicity; and complete denervation. Categorizing lower urinary tract function in this way has been extremely useful in predicting which children are at risk for deterioration of the upper urinary tract. Patients with sphincter dyssynergy and detrusor hypertony have a higher risk of ureterohydronephrosis, vesicoureteric reflux, pylonephritis and loss of kidney function. On the other hand, synergic voiders have a much better urological prognosis unless lower urinary tract function changes during childhood and adolescence. The neuro-urological lesion in myelodysplasia is a dynamic disease process with changes taking place during postnatal development. Once the spinal closure has healed sufficiently, renal ultrasonography should be performed as early as possible to detect renal dilatation. Following this, voiding cystourethrography and urodynamic study are conducted, especially if an ultrasound scan is abnormal. In the majority of cases, there is no need for intervention during the first month of life; however, a close follow-up is mandatory to progressively complete investigations with repeated ultrasonographies and to conduct renal scintigraphy, voiding cystography and urodynamic study. These investigations constitute baseline information for urological status in order to adapt follow-up treatment for infants at risk of urinary tract deterioration and who require initiation of prophylactic measures before the changes actually take place.

Urinary continence is becoming an increasingly important issue as parents try to provide a more mainstream life for their handicapped children. Conservative therapy includes school adaptations, strong nursing support, medication, and bladder intermittent catheterization. In most cases, urinary incontinence persists into early childhood at a level compatible with optimal social integration. In some cases, sphincter dyssynergy and detrusor hypertony are such that kidney deterioration occurs early in childhood, and they require bladder urinary diversion represented mainly by a vesicostomy. As "standard continence" is defined as continence encountered in unaffected individuals, it is clear that this level is rarely obtained in myelomeningocele patients. We should give preference to the term "social continence," which means the level compatible with integration into society and includes meaningful, long-term relationships. In this context, surgical indications for urinary incontinence treatment will result from a multi-faceted approach, encompassing urological and orthopedic considerations as well as the level of neurological impairment as well as personal and familial expectations.

6.3
Occult Dysraphism and the Tethered Spinal Cord

Children with cutaneous stigmata in the midline of the back, urogenitorectal malformation [27, 28], and congenital anomalies of the spine are known to harbor spinal cord anomalies that lead to deterioration in spinal cord function. Because the lesion is skin covered, it is classified as occult dysraphism [7]. Deterioration in spinal cord function was also observed in a second group of children with no visible stigmata of spinal disease. The common factor in these two groups of children is the presence of a fixed terminal end of the spinal cord with limited movement of the spinal cord in the cephalocaudal plane. The term "tethered spinal cord" signifies a pathological fixation of the spinal cord in an abnormal caudal location, so that the cord suffers mechanical stretching, distortion, and ischemia with daily activities, growth, and development. Such tethering can be caused by many conditions, including the tight filum terminale, spinal lipoma, myelocystocele, and arachnoiditis. Hydromyelia has proved to be a common accompaniment of cord tethering.

6.3.1
Spinal Lipomas

Congenital lumbosacral lipomas are the most frequent form of occult spinal dysraphism. They have been studied extensively, but uncertainties concerning the natural outcome of the disease, the true risks of surgery, and the quality of postoperative long-term outcome of patients remain a stumbling block to management of these lesions.

Spina bifida with lipoma represents a complex morphotype because it associates two single malformative processes: spina bifida and lipoma. The lipoma is made of adipocytes, connective tissue, and sometimes other types of structures [15]. Spina bifida and lipoma can be categorized into two groups: those characterized by a normal number of vertebrae and those associated with sacral agenesis. According to histological data, three subgroups of malformation can be distinguished: firstly, those in which the lipoma is made up of adipocytes and connective tissues only. In this case, the lesion is due to an impairment of the interactions between dorsal mesoderm and neurectoderm [5]. In the second group, dermoid or epidermoid cyst is present within the lipoma. This is due to an impairment of formation of the interepithelial space leading to an adhesion between the surface ectoderm and neural tube. This promotes development of the cyst. Furthermore, the interactions between dorsal mesodem and neural tube are defective, leading to formation of the lipoma. The third group of lipoma is characterized by cells that are not normally derived from the dorsal mesoderm (e.g., renal glomeruli, cerebellum, endometrium, and thyroid). Teratomatous cells could be present within the dorsal mesoderm. They could secrete factors preventing the normal differentiation of the dorsal mesoderm. Subsequently, this could lead to the formation of the lipoma. In contrast, spinal lipoma with sacral agenesis cannot be explained by the sole mechanism of abnormal development of the dorsal mesoderm. This phenotype belongs to the so-called caudal agenesis syndrome. It can be explained by an impairment of the normal movements involved in the formation of the embryonic axial body.

6.3.1.1
Anatomic Forms

Among the various anatomic forms of lumbosacral lipoma, lipomas of the filum should be distinguished from lipomas of the conus, the latter being not only much more frequent, but also much more complex, than the former.

6.3.1.2
Lipoma of the Filum

The fatty infiltration may involve the whole length of the filum or only part of it. Rarely, the lipoma has, along with the filum, an abnormal course, spreading out of the dura to extend subcutaneously. Roots of the cauda equina may adhere severely to the pia mater covering the lipoma, but generally are not malformed.

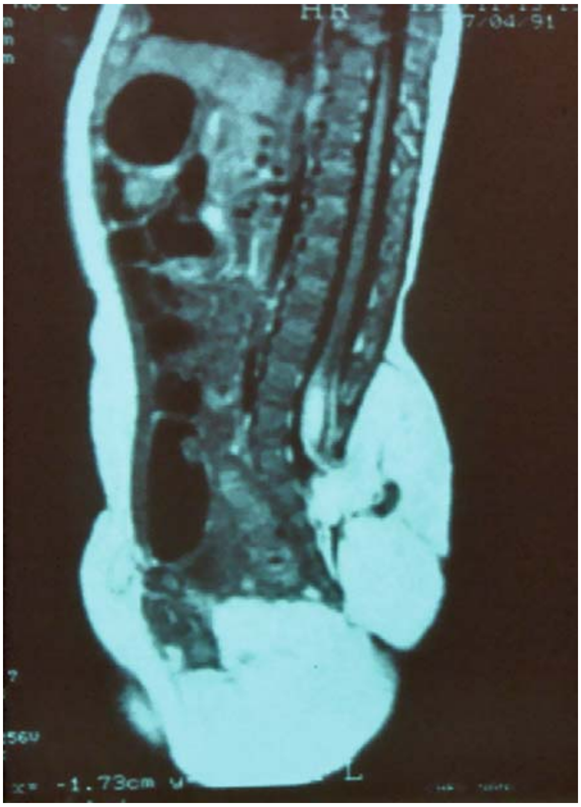

Fig. 4. Lipoma of the conus. Magnetic resonance imaging shows the sagittal view of a typical lipoma of the conus extending subcutaneously through the defect of a spina bifida.

6.3.1.3
Lipoma of the Conus

Different anatomic forms must be described, but all have in common the insertion of the lipoma on the terminal cord. In typical forms, lipomas of the conus spread out of the dura to extend subcutaneously through the defect of a spina bifida (Fig. 4). The volume of the intradural lipoma can be large and may compress the cord. In complex forms, the majority of cases, lipoma is associated with other neural tube defects. In lipomyelomeningocele, a subcutaneous meningocele is associated with the lipoma. In lipomyelocele, the cord extends extraspinally within the mass of the subcutaneous lipoma. In lipomyelocystocele, the terminal cord is the seat of a pseudocystic terminal hydromyelia closed superficially by the dura of the cul de sac, itself covered by the lipoma. Presacral lipoma is usually associated with sacral agenesis. Spinal lipomas may be associated with other malformations involving varying degrees of the cord (syringomyelia), the roots (intralipomatous roots), the spine (sacral agenesis, scoliosis), the skin [24], the urogenital tract, and other viscera [13].

6.3.1.4
Clinical Presentation

Clinical manifestations of lumbosacral lipoma are those of the so-called tethered cord syndrome [22]. The malformation is diagnosed early in childhood in the presence of cutaneous stigmata. In true occult dysraphism, diagnosis may be suggested when neurological symptoms appear, combining in various ways neurological deficits in the lower limbs, sphincter disturbances, and orthopedic deformities. The cutaneous syndrome groups skin anomalies representing a considerable diagnostic value. Their absence or discretion is generally responsible for delayed diagnosis. Cutaneous stigmata are usually located on the midline of the lower region of the back. It consists of sinus tract, skin tags, angiomas, cutaneous aplasia, caudal appendix, and patchy hair. Coccygeal dimples may be associated with subcutaneous lipomas. The current notion that isolated coccygeal dimples are never associated with a dysraphic state is not totally true. The neurological syndrome is extremely difficult to certify in neonates or infants, as well as neurological deterioration in adolescents. In the young child, sensory impairment, motor deficits when discrete and located to the plantar soles muscles, and voiding difficulties in the absence of clear incontinence, or repeated urinary infections, may remain clinically undiagnosed. Pain is reported less in the pediatric population than in adulthood. Persisting ambulatory instability, persisting incontinence, or development of a club foot may indicate a recent aggravation but may reveal as well a previously undiagnosed deficit. Sphincter disorders are the most common trouble. Incontinence results mainly from dysuria, pollakiuria, urgent micturation, and incomplete voiding. Urodynamic study frequently reveals hyperactive bladder and vesico-sphincteric dyssynergia. Bowel dysfunction consists of constipation with secondary stool leakage due to fecal retention.

6.3.1.5
Prognosis of Spinal Lipoma

Lipoma of the filum and lipoma of the conus have very different prognoses, the former being more easily treated. Surgery is without complication in the treatment of lipomas of the filum, but difficult and hazardous in the case of lipomas of the conus. All types of deficit could be improved by surgery, which was beneficial in all cases of lipoma of the filum and 50% of cases of lipoma of the conus. In asymptomatic patients long-term surgical results depend on the anatomical type of the lipoma. The results were excellent in lipomas of the filum but in lipomas of the conus, the results were good in the short-term but eroded with time. Five years after surgery, only half of the patients remained free of symptoms.

Prenatal assessment of fetal spinal dysraphism and myelodysplasia is a key point in parental counselling. The distinction between meningomyelocele and spinal lipoma [8, 22] is possible antenatally [26]. The differential diagnosis between lipoma and the other forms of occult dysraphism is more difficult. Whether or not prenatal MRI may add more information than prenatal ultrasonography in categorizing myelomeningocele and spinal lipoma remains unanswered.

6.3.2
Other Occult Spinal Dysraphism

6.3.2.1
Dorsal Dermal Sinus

Clinically, dorsal dermal sinuses appear most frequently as pinpoint holes in the skin of the midline (Fig. 5). Small hemangiomas commonly surround the ostium. A tuft of short sparse wiry hairs may protrude from the ostium. Dermal sinuses frequently provide a path through which infection may ascend retrogradely into the spinal canal. Such infection may lead to arachnoiditis, meningitis, and abscess. Typically, the dermal sinus tract extends inward from the skin surface to a variable depth. It passes deeply through the subcutaneous layer and through the median raphe (or between bifid laminae) toward the dura. It may end at or before the dura. In most cases, the tract extends into the spinal canal deep to the dura. The tract may end in the subarachnoid space as an open tube through which CSF discharges. The dermal sinus may also end in a fibrous nodule lo-

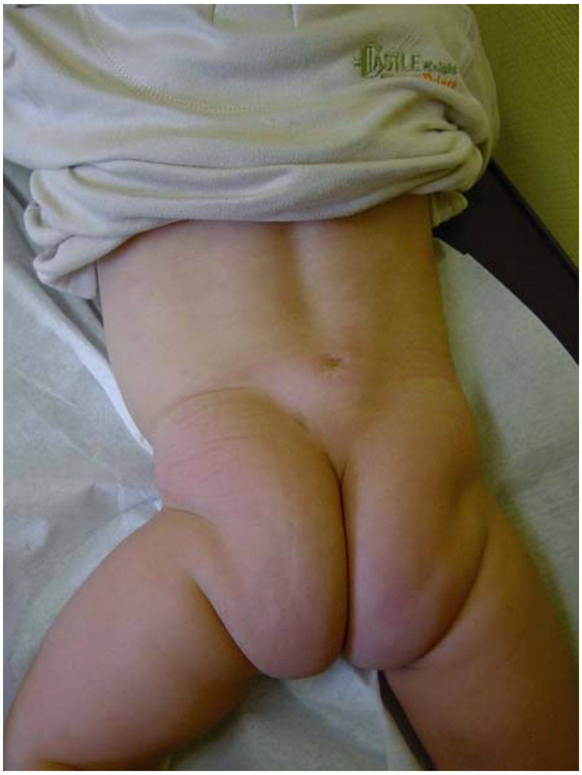

Fig. 5. Occult spinal dysraphism with closed dermoid sinus overlaying a spinal lipoma

cated among the roots of cauda equina. In up to 60% of cases, the tract incorporates or ends in a dermoid or epidermoid tumor. Approximately 30% of all spinal (epi)dermoids are associated with dermal sinuses. The dermal sinus may cause tethering by a thick band of tissue attached to the conus or as a result of the scarring produced by bacterial meningitis. Magnetic resonance imaging displays the extraspinal course of the dermal sinus as a low-signal tract that transverses the high-signal subcutaneous fat toward the dura. Magnetic resonance imaging does not readily show the intradural course of the tract itself. Dermoid tumors have highly variable signal intensity on MRI and must be sought diligently with different pulse sequences to ascertain their presence.

6.3.2.2
Tight Filum Terminale Syndrome

Patients with the tight filum terminale syndrome present the same clinical signs as tethered cord presented in spinal lipoma. In such cases, the spinal cord must be tethered, the filum must measure more than 2 mm in diameter, and no other cause for tethering should be present. The tip of the conus medullaris lies below L2 in most cases. The spinal cord may continue to attach caudally to the distal thecal sac without distinct termination. In one-third of cases, filar fibrolipoma is present. Kyphoscoliosis may be present and improves following section of the filum in one-third of cases. Usually there is a midline defect in the arches of the lumbosacral spine, typically at the L4, L5, and/or S1 level. This suggests that a normal spinal radiograph could almost exclude this diagnosis; however, several series have been reported of children with incontinence and essentially a normal MRI, whose condition improved following section of the filum terminale. Such children usually have urodynamic findings consistent with a neurogenic bladder. The MRI reveals a conus at or near the normal level, and the filum appears either normal or to contain a small amount of fat. There have been reports of patients with tethered cord syndrome who, using myelography, computed tomography, or MR imaging, have shown a normal cone shape and location, as well as those with an abnormally low cone location without obvious tethering causes. In such cases, additional information, such as dynamic information obtained at standard MR imaging, is needed to make a definitive diagnosis. The spinal cord normally exhibits anteroposterior and cranio-caudal movement in MR imaging, whereas the tethered spinal cord exhibits its decreased or no movement [30]. Prone MR imaging has no additional value when the supine MR image has clearly shown the cause of tethering, or in patients who have undergone tethered cord surgery, but it can provide additional information in patients clinically suspected of having a tethered cord and in whom supine MR imaging depicted no abnormalities.

6.3.2.3
Diastematomyelia

Diastematomyelia signifies sagittal clefting of the spinal cord, conus medullaris, and/or filum terminal into two – not necessarily symmetric – hemicords. The genesis of diastematomyelia is unknown. Persistence of an accessory neurenteric canal that traversed the notocord and neural plate explains the concurrence of the multiple-segmentation anomalies, hemivertebrae, spina bifida, skin lesions, cleft dura and cord, and associated midline cysts and tumors. Cutaneous naevi overlie the midline of the back in some cases. The most characteristic cutaneous stigma is a large patch of long silky hairs. Scoliosis and kyphosis are present in 50–60% of cases and are related directly to the segmentation anomalies. Whereas the kyphoscoliosis of myelomeningocele is typically neurogenic, the kyphoscoliosis of diastematomyelia is typically mechanical. The extent to which cord tethering contributes to the scoliosis is unclear, and nearly 50% of patients with diastematomyela also have hydromyelia, which may contribute to progression of the scoliosis. The conus medullaris is usually low in position. The two hemicords are each narrower than normal and nearly always reunite distally to reform a single spinal cord below the cleft. The filum terminale is almost always thickened, may itself tether the cord, and may require section for release of tethering.

6.3.3
Sacral Agenesis

Sacral agenesis has been defined as absence of part or all of two or more lower vertebral bodies. The etiology of this condition is still uncertain. The diagnosis is often delayed unless other abnormalities are present. When isolated, the diagnosis is delayed until failed attempts at toilet training. Sensation, including perianal dermatomes is usually intact, and lower limb function is normal. The only clue is flattened buttocks and a low short gluteal cleft. Palpation of the coccyx detects the absent vertebrae. The diagnosis is most easily confirmed with a lateral film of the lower spine, because this area is often obscured by the overlying gas pattern on an anteroposterior projection. Sacral agenesis is often associated with other abnormal conditions mostly included in the VACTERL syndrome [29]. This mnemonic stands for all of the organs that possibly can be affected (V=vertebral, A=anal, C=cardiac, TE=tracheo-esophageal fistula, R=renal, L=limb). Currarino's syndrome [9] involves sacral agenesis, presacral mass, and perineal malformation. The presacral mass may be a meningocele, teratoma, enteric cyst, or lipoma. This syndrome presents some analogies with those of caudal regression, which is associated with various malformations of the lumbosacral spine, lower limbs, and urogenitoanal tract.

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Neurologic Bladder in Neuropathies

7

Ciro Esposito · Girolamo Mattioli · Vincenzo Jasonni

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7.1
Introduction

Bladder control is ensured by an integrated function of the brain, brainstem, spinal cord, and peripheral nervous system. Various impairments of this function, due to diseases involving one or more organs of the nervous system, may be the cause a neurogenic bladder, via damage of the parasympathetic, sympathetic, or nerve supply to the bladder [1, 2, 4].

The parasympathetic nerves control detrusor contraction via the nervi ergentes from root S2–S4 of the spinal cord. The sympathetic source, which innervates the trigone and the internal sphincter, ensures the opening of the bladder neck during the micturition.

The pudendal nerve ensures the voluntary control of the striated external sphincter. Damage to the bladder nerve supply is a frequent condition underlying many forms of neuropathy [5, 22]. Neuropathies, also referred to as peripheral neuropathies, present as a form of complex syndromes, although a given disease may affect only one nerve (single mononeuropathy) or more nerves in an asymmetric and synchronous manner (polyneuropathies). They are characterized by functional insufficiency of the motor, sensory, and autonomic nervous system, and present as a sensory-motor disorder and, eventually, as disorders of the autonomic system of many organs or apparatuses.

Single mononeuropathies generally have a genetic or inflammatory origin; multiple mononeuropathies may have a vascular, metabolic, infectious, or compressive origin; polyneuropathies due variable causes may also be an epiphenomenon of diseases of various etiologies.

Many classifications for neuropathies have been proposed; one of the most complete ones is that by Cali and Fiore-Donati, which includes hereditary neuropathies, neuropathies of immune origin, toxic neuropathies, neuropathies due to deficiencies, paraneoplastic neuropathies, metabolic neuropathies, infectious neuropathies, ischemic neuropathies, and, lastly, neuropathies due to traumatic injury of the nerves [6, 10, 18, 19, 21].

The classification proposed by Nappo is also quite comprehensive, and includes neuropathies due to physical agents, neuropathies occurring during a systemic disease, poisonous neuropathies, neuropathies due to nutrient deficiency, inflammatory neuropathies, infectious neuropathies, genetic neuropathies, neuropathies in elderly people, and, lastly cryptogenic neuropathies.

A simpler classification has been provided by Gaburro and collaborators; it includes inflammatory neuropathies, hereditary neuropathies, toxic neuropathies, and neuropathies due to traumatic injury of the nerve [1, 2, 4].

Only some neuropathies lead to disorders of the autonomic nervous system and involve various organs or apparatuses. In this chapter, for the sake of completeness and to provide the reader with a broad view for differential diagnosis, we describe synthetically all the types of neuropathies, but we illustrate in detail the neuropathies accompanying the disorders of the autonomic nervous system of the bladder that manifest with the classical symptoms of neuropathic bladder [5, 22].

7.2
Hereditary Neuropathies

Hereditary neuropathies, generally referred to by the acronym HMSM (hereditary motor and sensory neuropathies), are genetically well-defined, progressive diseases of the peripheral nerves. They include hereditary motor neuropathies, hereditary sensory-motor neuropathies, and a mixed group of primitive and secondary neuropathies with peculiar features for each specific form.

Hereditary motor neuropathies include four groups of neuropathies; their onset and transmission characteristics are reported in Table 1.

7.2.1
Hereditary Motor and Sensory Neuropathies

Hereditary motor and sensory neuropathies are represented essentially by the Charcot-Marie-Tooth disease (CMT), which is a chronic, dominant or recessive inherited condition frequently associated with submicroscopic duplication of DNA at the proximal tract of chromosome 17. It is characterized by peripheral motor, sensory, and autonomic involvement with onset during school age and adolescence [18]. Regarding its clinical, genetic, pathological, and electrophysiological characteristics, there are various forms of CMT: precisely a myelinic form (CMT1 with two subgroup CMT1a and CMT1b) and an axonal form (CMT2). The first type is characterized by early onset, with reduced nervous conduction speed, and a pathological feature of hypertrophic neuropathy with onion-bulb formation. The second form is characterized by late-onset, normal conduction speed but a pathological reduction of the number of fibers, by nerve fibers with greater diameter, and by regeneration processes. Clinically, the motor disorders present with muscular weakness, areflexia, peroneal atrophy, and hollow foot.

Sensitive disorders are represented by paresthesias, sharp pain, cramps, and reduced perception of light touch or vibrations. Autonomic disorders consist of hypotension, bladder dysfunction, and erectile dysfunction. Bladder dysfunction manifests with urinary urgency or incontinence, dysuria, urinary infectious, and sometime urinary lithiasis. At the cystometrogram, there is a markedly reduced flow, elevated post-void residue, and detrusor hyporeflexia.

Similarly to other bladder disorders due to other diseases, the treatment of choice is intermittent catheterization associated with antibiotic prophylaxis or treatment of urinary infections.

The neuronal form of muscular peroneal atrophy very much resembles late-onset CMT, with mild involvement of hand nerves and frequent involvement of sensory nerves.

The spectrum of urinary symptoms of CMT roughly resembles that of the Machado-Joseph disease (MJD), from which it should be differentiated. The MJD is a hereditary spinocerebellar ataxia of genetic nature, characterized by cerebellar ataxia, associated with various combinations of pyramidal spasticity, extrapyramidal rigidity, dystonia–atetosis, ophthalmoplegia, and sensory impairment [15].

The urinary disorders are the same as for MCT: nocturnal and diurnal frequency; urinary urgency and incontinence; and voiding difficulty and urinary retention.

7.2.2
Sensory and Autonomic Neuropathies

Sensory and autonomic neuropathies are represented by ulcerative mutilating acropathy and by congenital insensitivity to pain; the first is characterized by the formation of trophic ulcers and by distal chronic disturbance, and may have a dominant transmission (NES1) or a recessive transmission (NES2); the second includes various forms of neuropathies, the most important being familiar dysautonomia or Riley-Day's disease or syndrome. This specific condition is characterized by

Table 1. Hereditary motor neuropathies in pediatric age

	Type	Beginning	Transmission	Eponym
Muscular spinal atrophy	I	Infantile precocious	Autosomal-recessive	Werdning-Hoffmann disease
	II	Infantile	Autosomal-recessive	Werdning-Hoffmann disease
	III			
	IV			
Scapolo-umeral atrophy		Infantile	Autosomal-recessive	–
Spinal bulb atrophy		Juvenile	Related to one chromosome X	Kennedy disease
Muscle bulb atrophy	I	Infantile	Autosomal-recessive	Fazio-Lande disease
	II	Juvenile	Autosomal-recessive	Vialetto-von Laeer disease

the degeneration or disappearance of the small neurons of the distal ganglions and by a reduction of the amyelonic fibers and the disappearance of myelonic fibers with larger diameter.

It is a mainly autonomic neuropathy and is also called idiopathic autonomic neuropathy [8, 10, 14, 16]. As to the clinical features, the spectrum of autonomic changes is very heterogeneous, ranging from cholinergic or adrenergic dysfunction to pandysautonomy [7]. In fact, like all diseases of the autonomic nervous system, it gives rise to many types of impairments involving blood pressure, heart rate, temperature regulation and sweating; bladder, sexual, and gastrointestinal function; lachrymal glands and pupil function.

Among the clinical features, there are postural dizziness, syncope, dry mouth and eyes, gastro-esophageal reflux, incontinence or bowel urgency, constipation or diarrhea, anhydrosis or focal hyperhydrosis, and excess sensitivity to heat or coldness of the limbs. Bladder dysfunction is extremely marked and consists of loss of high central control of the bladder, impaired coordination of the detrusor muscle, and sphincter reflex function. These abnormalities may cause bladder overdistention, increased post-void residual urine volume, urinary retention, overflow incontinence, and may predispose to urinary infection.

Concerning the management of bladder dysfunction due to autonomic neuropathy, its most effective form of treatment is clean intermittent self-catheterization. The advantages of this treatment are the maintenance of low-bladder pressure, sufficient micturition, and voluntary control of bladder emptying [22].

Although the incidence of severe urinary infection is very low with this technique, the chronic bacteriuria associated with it requires careful monitoring through urinalysis, urine culture, and, possibly, antibiotic prophylaxis. In selected patients surgery may be useful, consisting of a sphinterotomy or a bladder neck resection and, should these fail, artificial urinary sphincter placement.

In relation to hereditary neuropathies, familial paralysis due to compression, familial amyloidosis neuropathy, hypertrophic juvenile neuropathy or Dejerin-Sottas disease, Refsum's disease, giant axonal neuropathy, acute intermittent porphyry, Krabbe's disease, and metachromatic leukodystrophy must also be mentioned.

Familial paralysis due to compression, or tomacular neuropathy, is an autosomal-dominant mononeuropathy caused by compression of the trunks, presenting with episodes of paralysis limited to a single nerve plexus (more frequently the brachial one). From the pathological point of view there is a thickening of the myelonic sheath with an onion-bulb formation (from which comes the term *tomacular*, from Latin), demyelinization, and/or disappearance of nerve fibers [10].

Familial amyloidosis neuropathy is an autosomal-dominant condition caused by the disappearance of myelonic and amyelonic fibers associated with endo- and perineural amyloid deposits. It presents with two clinical forms: (a) chronic amyloidosis neuropathy; and (b) amyloidosis neuropathy with carpal tunnel; the first is characterized by sensitive symptoms (paresthesias and pain involving the lower limbs) and autonomic ones (orthostatic hypotension, sphyncterial disorders not limited to the bladder), whereas motor symptoms are rare [14]; the second is characterized by the hypertrophy of the median nerve in the carpal tunnel. It has a more benign evolution compared with the first one, which is, instead, generally fatal due to amyloid infiltration into the kidney, followed by kidney failure.

Hypertrophic juvenile neuropathy or Dejerin-Sottas disease manifests in the first year of life and is caused by the fissuration of the myelonic sheaths of many nerves with nervous hypertrophic onion-bulb formations. The clinical signs are psychomotor retardation, muscular weakness, perambulation difficulties. Some authors consider it a variation of MCT [16].

Refsum's disease is an ataxic polyneuritiform hereditary condition. It is associated with central nervous system conditions caused by impaired peroxisome biogenesis. It is due to a deficiency of phytanic-α-hydroxylase acid which causes phytanic acid to deposit on the nerves, leading to hypertrophic neuropathy.

Giant-axonal neuropathy, as the previous type described, is associated with pathologies of the central nervous system and is characterized by the same hypertrophic neuropathy [5, 10].

Acute intermittent porphyry is a metabolic hereditary syndrome characterized by an excess of various porphyrins (erythroporphyrins, hepatoporphyrins) associated with an excessive urinary excretion of this chemical. Neurological symptoms are represented by ataxia, paresthesias, and paralysis of back and limb muscles.

Krabbe's disease is a sphingolipidosis, a genetic disease (autosomal-recessive) characterized by the lysosomal accumulation of sphingolipids due to a deficiency of the specific enzymes assigned to their breakdown. The enzymatic defect is at the level of the galactocerebrosidasis. It begins in the first month of the life with psychomotor deterioration, hypertonia, opisthotonia, optic atrophy, and convulsions [16].

The metachromatic leukodystrophy or Scholz-Greenfield disease is, as Krabbe's disease, a sphingolipidosis caused by a deficiency of arilsulfatase A, which causes the accumulation of a cerebroside-sulfate on the white substance of the nervous tissue and of peripheral nerves [14]. There are two form of this disease: the infantile form that begins during the second year of life with regression of psychomotor development, tetraparesis, tetraplegia; the second one, the juvenile form, begins after the third year of life with behavioral disorders.

7.3
Inflammatory-Immune Neuropathies

Inflammatory-immune neuropathies is represented by idiopathic acute infectious polyradiculoneuritis, neuropathy during paraproteinemia, and Bell's paralysis. The idiopathic acute infectious polyradiculoneuritis, or Guillain-Barré-Strohl syndrome, may have an acute or subacute presentation, with onset a few days or weeks after a viral infection, a vaccination or a surgical operation.

It is probably due to an autoimmune mechanism with production of antimyelin antibodies that attack the roots and the proximal tract of the peripheral nerves causing endoneural edema, and lymphomonocytic infiltration of the plasma membrane of the Schwann's cell responsible for the asymmetric and segmental demyelinization [10, 16]. The disease is characterized by parestesias of the extremities, with weakness of the four limbs, followed by an ascending progressive flaccid paralysis with tendineous areflexia. The involvement of chest muscles may be responsible for severe respiratory insufficiency.

A common variant of this syndrome is the Miller-Fisher syndrome, which presents with ataxia, areflexia, and external ophthalmoplegia.

Idiopathic chronic recurring polyradiculoneuritis presents the same biological characteristics of the acute form. It is probably due to an autoimmune mechanism of genetic origin. It is characterized by processes of demyelinization and remyelinization that evolve toward hypertrophic neuropathy with complex onion-bulb formations [16].

7.3.1
Neuropathy During Paraproteinemia

Paraproteinemias are characterized by the presence of an anomalous band of gammaglobulins. A myeloma or a macroglobulinemia of Waldenstrom may be the underlying cause of this peripheral symmetric sensory-motor neuropathy. The evolution of this condition is slow and is due to the injuries by autoantibodies against the glycoprotein associated with the myelin [10].

Bell's palsy is a monolayer acute paralysis of the facial nerve. It is the most frequent post-viral neuropathy due to the Epstein-Barr virus. On an immune-allergic basis it causes the demyelinization of the facial nerve that presents with the characteristic paralysis of this nerve [10].

7.4
Toxic Neuropathies

While neuropathies due to heavy metals or organic substances are rare in pediatric age, those caused by drugs are, on the contrary, frequent.

7.4.1
Neuropathies Due to Heavy Metals

Neuropathies due to heavy metals are due essentially to lead, arsenic, mercury, and thallium. Neuropathies due to lead involve mainly the extensor of the forearm, although they may cause axonal degeneration with segmentary demyelinization in any part of the body [20]. Exposure to arsenic may lead to axonal neuropathy with degeneration and disappearance of the fibers. Mercury causes a mixed sensory-motor neuropathy of axonal type. Neuropathy due to thallium is caused by a swelling of the mitochondria, with disappearance of the inner substance and formation of numerous vacuoles [21].

7.4.2
Neuropathies Due to Organic Substances

Neuropathies due to organic substances include neuropathies from the exposure to hexane, carbon sulfide, acrylamide, organic phosphors, cyanide, trichloroethylene, and triortocresilphosphate. The most important neuropathies are:

1. Those due to hexane, which through its neurotoxic metabolite (2-5-hexandione) causes multimodal swellings of the axons
2. Those due to carbon sulfide, presenting with lesion similar to those caused by hexane
3. Those due to acrylamide are responsible for axonopathy with axonal and myelinic degeneration
4. Those caused by organic phosphorus are responsible for axonal neuropathies with the distal–proximal evolution [20, 21].

7.4.3
Neuropathies Due to Drugs

Contrarily to the previous neuropathies, which are generally frequent in adults, these are more common in pediatric age as a consequence of the diffusion of antineoplastic chemotherapy. Several drugs are responsible for these neuropathies, and include choramphenical, isoniazid, vincristine, gold, hydrozide, phenilhydantoin, metronidazole, disulfiram, cyclophosphamide, cysplatinum, and oxilplatinum [20, 21].

Of particular interest are the neuropathies caused by isoniazid, for the characteristic pathological features of axonal lesions associated with a simil-wallerian degeneration. The sensory-motor neuropathy due to vincristine is characterized pathologically by axonal and myelonic degeneration; the ones caused by cyclophosphamide are responsible for a peripheral sensory-motor polyneuropathy. Oxilplatinum is responsible for cold-induced distal paresthesias occurring during the short treatment or a persistent peripheral sensory neuropathy that may develop with prolonged treatment producing surface and deep sensory loss, sensory ataxia, and functional impairment. During treatment with oxilplatinum an atonic bladder may occur as a result of damage to the sensory position of the sacral reflex either in the posterior column or in the dorsal roots or, alternatively, micturition difficulties due to a paralysis of the parasympathetic fibers [20].

The findings of an impaired peripheral sensory function involving both the sympathetic and sensory peripheral innervation have been confirmed experimentally by cysplatin administration in rodents.

7.5
Neuropathies Due to Deficiencies

They include beriberi neuropathy, alcoholic neuropathy, and pellagra neuropathy. Neuropathy due to beriberi is a sensory-motor neuropathy with cardiac involvement due a thiamine-deficient diets. From the pathological point of view, it is an axonal neuropathy with simil-wallerian degeneration of the fibers especially involving the distal part of the nerves [13].

Neuropathy due to non-alcoholic thiamine deficiency may be responsible for a Gayet-Wernicke type encephalopathy, but rarely for a bladder dysfunction with detrusor hypereflexia and detrusor–sphincter dyssynergy with natural micturitions of increased urinary volumes and increased post-void remains.

From the urodynamic point of view we may find a hypoesthetic and hypoactive bladder of great capacity with a basal tone of almost 10 cm at 60 ml/min at cystometry. This bladder dysfunction may be associated with disturbances in bladder sensitivity. It is associated with a favorable prognosis considering that thiamine supplements cause a rapid regression of the symptoms.

In case of beriberi in alcohol drinkers or in people living in areas characterized by thiamine-deficient diets, the diagnosis of neuropathy should be confirmed by measuring serum thiamine levels, which should be below 3 nmol/l (normal: 6–40 nmol/l) [13].

Alcoholic neuropathy is rare in pediatric age, but may occur in adolescents. It is a mixed sensory-motor neuropathy due to a deficiency in multiple elements (thiamine, folic acid, pyridoxine, etc.) and is responsible for the disappearance of fibers and for axonal degeneration.

7.6
Paraneoplastic Neuropathies

This category of paraneoplastic neuropathiesincludes sensory ganglioradiculoneuropathy and sensory-motor neuropathy [2]. the first is caused by several types of neoplasias (especially pulmonary mycrocytoma), and manifest with paresthesias and pain, especially at the lower extremities. It is caused by lesions of the ganglions, roots, and nerve trunks, most likely on an autoimmune basis [10]. The second type, also with an autoimmune pathogenesis, occurs in various types of neoplasias (ovary, colon, lung, breast, etc.) and presents with the pathological findings of axonal degeneration with segmentary demyelinization [10].

7.7
Metabolic Neuropathies

Metabolic neuropathies include diabetic neuropathy and uremic neuropathy. Diabetic neuropathy may present as single or multiple mono-neuropathy or as symmetric neuropathy, which may be sensory-motor, distal, pure sensory, or pure autonomic [9, 11, 12]. The nervous lesions are represented by the disappearance of myelinic fibers as well as amyelinic and simil-wallerian degeneration. Their pathogenesis is not completely defined, although an ischemic or vascular phenomenon has been hypothesized.

Autonomic dysfunctions are common in diabetes, whereas symptomatic autonomic neuropathies, which are classified as clinical or subclinical, are rare. The symptoms may involve the cardiovascular, gastrointestinal, genitourinary, or the neuroendocrine systems. As to the genitourinary tract, symptoms may be a neuropathic bladder, recurrent urinary infections, urinary retention, nephropathy with significant proteinuria and renal impairment, disturbance of urinary voiding and, at cystometry, decrease in detrusor pressure or absence of detrusor contractions, and detrusor–sphincter dyssynergia [17, 19, 22].

The pathological finding in cases of uremic neuropathy typical of renal insufficiency is that of axonal lesion with simil-wallerian degeneration and disappearance of fibers.

7.8
Infectious Neuropathies

Infectious neuropathies include diphtheritic neuropathy, leprous neuropathy, Herpes-Zoster neuropathy, HIV neuropathy, neuropathy caused by Lyme's disease, neuropathy due to sarcoidosis and neuropathy due to infectious mononucleosis [2].

Diphtheritic neuropathy, caused by the demyelinization of peripheral nervous trunks, has virtually disappeared since the introduction of the obligatory vaccination against diphtheria.

The leprous neuropathy of different degrees of severity may be due to either tubercular leprosy or to lepromatous leprosy. In the first case, the leprous granuloma affects the nervous trunks which present with no fibers and increased endoneural collagen, whereas in the second case there is a bilateral symmetric involvement of the peripheral nervous system, with no axons and segmentary demyelinization [3, 6].

The neuropathy of HIV includes various forms in relation to the phases in which they manifest. In the seroconversion phase the inflammatory demyelinizating polyneuritis is frequently associated with weakness of the extremities and district paralysis. In the subsequent phase of infection, it manifests with distal symmetric polyneuropathy and, eventually, with multiple mononeuropathy.

The neuropathy that manifests during Lyme's disease (or Garin-Boujadoux-Bannworth's syndrome) is due to the spirochete *Borrelia Burgdoferi*, which is transmitted by the tick *Ixodes Dammin*. The involvement of the peripheral nervous system occurs only in the chronic forms of the disease, such as mono- or polyradiculoneuropathies and has features such as those of the Guillain-Barré-Strobe's syndrome.

The Herpes-zoster neuropathy may be accompanied by bladder dysfunction in relation to the involvement of the sacral, thoraco-lumbar, and thoracic dermatotomies responsible for a sensory-motor neuropathy [6].

Bladder disorders consist of urinary retention and interruption of the detrusor reflex, causing subsequently bladder atonia.

The neuropathy that manifests during infectious mononucleosis, due to Epstein-Barr virus, resembles the symptoms of the Guillain-Barré syndrome or those of transverse myelitis [2, 6].

7.9
Ischemic Neuropathies

Ischemic neuropathies are due to vasculitis, which is a frequent finding during various diseases such as periarteritis nodosa, rheumatoid arthritis, Wagener's granulomatosis, and are generally simple or multiple mononeuropathies caused by the disappearance of nerve fibers [1, 2]. Neuropathies due to traumatic lesion of the nerve may be acute or chronic. Acute lesions present three stages: neuropraxia; axonotmesis; and neurotmesis. The neuropraxic stage is responsible for the nervous conduction block due to demyelinization or to a focal edema. The axonotmesis consists of the interruption of the axon with wallerian distal degeneration [2]. The neurotmesis consists of the interruption of the fibers with formation of an amputation neuroma.

Chronic lesions are due to compression of the nerves inside an anatomic channel. The ensnarement of the median nerve in the carpal tunnel and the ensnarement of posterior tibial nerve in the tarsal tunnel are noteworthy.

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Pediatric Intraspinal Lesions

8

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8.1
Introduction

Intraspinal lesions include a great variety of histological types including tumors developed inside the central canal of the spine. These tumors can be intradural or epidural, and tumors originating from the vertebra. A peculiar aspect is represented by dysembryoplastic tumors which are not true neoplasms, but their behavior is the same as that of intraspinal tumors. They include several dysraphic lesions included in occult spinal dysraphisms. These lesions are the consequence of an incomplete closure of the midline structure of the dorsum, and lesions as different as lipomas, dermal sinus, dermoid cysts, and neurenteric cysts can be encountered. Most of them are located in the lumbar region but can be found at any level of the spine.

Intraspinal tumors can be classified anatomically by location with respect to the dura and the cord. Intramedullary tumors develop inside the parenchyma, like extramedullary lesions, can be epidural or intradural (Table 1). Extension of bone tumors can compromise the cord or the roots.

Table 1. Location of Intraspinal Tumors in authors’s series of 203 cases

Intramedullary tumors	68
Intradural-extramedullary tumors	42
Extradural tumors	47
Vertebral tumors	46

This chapter is based on the authors’ experience who managed more than 320 dysraphic lesions and 203 intraspinal tumors in children.

8.2
Clinical Presentation

The clinical manifestations of true tumors must be distinguished from those of dysembryoplastic tumors. Indeed, a long course of spinal pain and/or “orthopedic” scoliosis is usually observed in 30–60% of the cases for intramedullary and intradural tumors [6, 8, 20]. On the other hand, sphincter disturbances are very rare, except for tumors located at the level of conus medullaris and the cauda equina, which represent a very low incidence of these tumors. Motor regression, which is frequent in true tumors, is observed in 60–80% of the children [6, 8, 20].

For dysembryoplastic tumors, clinical manifestations can be classified into four groups:

1. Cutaneous signs can be visible at birth and have been observed in 70% of the cases in our series of 356 lumbar dysraphisms at this age. In the literature, their incidence varies between 73 and 93%, and was 92% in our series [5, 14, 17]. These signs can be also variable as lipomatous mass, skin dimple, dermal sinus, capillary naevus, and appendage.
2. Orthopedic manifestations, the incidence of which is estimated to be 9–50% in the literature, and was 34 % in our series. They are usually observed in older children or teenagers, and occur only rarely in infan-

cy. Scoliosis, kyphosis, spinal malformations, limb shortening, and foot or toe deformities are the classic signs.

3. Neurological symptoms, such as motor deficit, amyotrophia, and mal perforans, are observed in 10–45% of cases (19% in our experience) and are observed in older children [5, 14, 17]. Bacterial meningitis can reveal an intradural dermoid or neurenteric cyst.
4. Sphincter manifestations are present in 10–45% of cases (18.5% in our series) [5, 14, 17]. Urological symptoms, such as incontinence or frequent micturition, are frequently associated with urinary infection. Incontinence of feces is very rare and is usually observed in older children.

Rarely the dysembryoplastic tumor can be included in a syndromic condition such as Currarino syndrome [7]. We have observed four cases in our series of spinal dysraphisms.

8.3
Neuroimaging Techniques

Magnetic resonance imaging has replaced invasive radiodiagnostic studies [21]. Myelography has little use in the investigation of intraspinal lesions, whatever their precise location, and can be reserved for patients with metallic spinal implants where artifacts do not allow a correct evaluation. A CT scan and MRI scan are indicated for spine lesions. Axial and sagittal views on T1- and T2-weighted images allow correct analysis of the relationships between the lesions and the spinal cord, the roots of the cauda equina and the dura.

8.4
Pathology

Whatever the precise location of the lesions, a wide spectrum of pathology is observed.

8.4.1
Intramedullary Spinal Cord Tumors

At any age, >80% of intramedullary spinal cord tumors (Table 2) are astrocytomas and ependymomas, but the pathology differs with age. Indeed, astrocytomas predominate in children [13, 20, 26, 35], at reverse ependymomas are much more frequent in adults. Tumors of disordered embryogenesis [27], such as lipomas, dermoids/epidermoids, teratomas, and neurenteric cysts, are observed especially in children.

Table 2. Histologic types of IMSCT'S tumors observed in Authors's Series (68 cases)

Pathology	No. of Patients
Glioma	
Low-grade	28
High-grade	12
Ependymona	13
Ganglioglioma	3
Lipoma	3
Dermoid/Epidermoid	3
Neurenteric cyst	1
Vascular sarcoma	1
Malignant meningioma	1
Metastasis (Neuroblastoma)	1
Cavernoma	2

8.4.1.1
Astrocytomas

Astrocytomas represent the most common tumors encountered in children. The great majority of them are low-grade astrocytomas, which are benign tumors (28 cases in our series), but very few are located in the caudal part of the cord. The MRI study shows usually a solid portion and a caudal and rostral cyst which delimit the part of the tumor to remove. The surgical problem is due to the absence of a true plane of dissection between the tumor and the adjacent tissues [6, 32, 35]. Presently, the prognosis of high-grade astrocytomas still remains very poor, whatever the adjunctive therapies proposed [2, 9, 20, 23].

8.4.1.2
Ependymomas

Ependymomas are the second most common tumors observed in children, but their elective location is the cauda equina. Whatever their precise location, intramedullary or cauda equina, 90% of these tumors are amenable to complete removal [3, 4, 22, 24, 28]. The prognosis of the tumor is correlated with the extent of resection [3, 22, 24]. Due to the deleterious effect of radiotherapy on the growing spine, it can be indicated only for giant tumor located at the level of cauda equina in case of residue after removal [19, 29].

8.4.1.3
Miscellaneous

Many other tumoral types are observed, but particular to children are dysembryoplastic tumors [1, 7, 18, 20, 31, 34], such as lipomas, dermoid/epidermoid tumors, and neurenteric cysts which can be located at any level of the cord. In our experience, we have operated on three lipomas localized at the cervical (2 cases) and thoracic (1 case) levels, respectively, and three dermoid/epidermoid cysts at the level of cauda equina invading the conus and carrying a neurogenic bladder dysfunction.

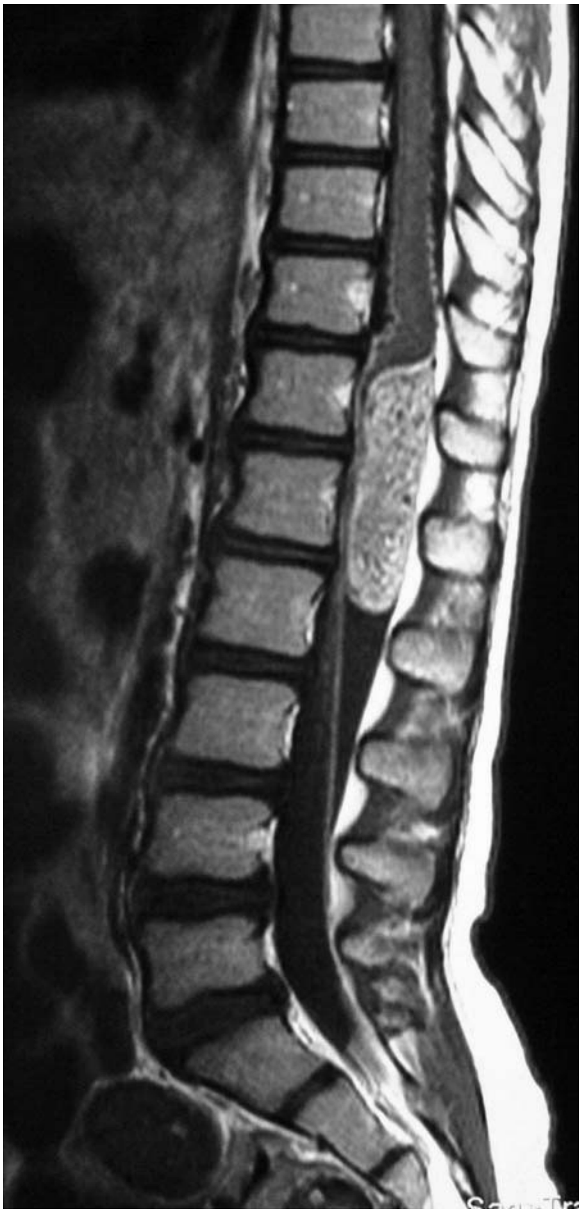

Fig. 1. Ependymoma of the filum terminale invading the conus medullaris. T2-weighted image on sagittal view after contrast enhancement

8.4.2
Intradural Extramedullary Tumors

8.4.2.1
Ependymomas of Filum Terminale

Although rare, ependymomas of filum terminale represent the most common tumor encountered at this level [4, 11, 28]. Before the advent of MRI, this tumoral type was usually diagnosed at the stage of giant tumor and total removal was rarely possible. From a pathological point of view, a typical aspect of myxopapillary benign ependymoma (see Fig. 1) is observed, and the cure can be obtained with a radical removal. Radiotherapy is only indicated for residual tumor.

8.4.2.2
Schwannomas and Neurofibromas

Schwannomas and neurofibromas are rare tumors. In children, they are frequently observed in patients suffering from neurofibromatosis type 2 (7 cases in our series). The most common symptom is radicular pain exacerbating during the night and urological signs are usually absent. They can be located at any level of the spinal canal, but above all at the level of cauda equina (6 cases). Radical removal of these tumors is almost always possible, which can lead to cure, but recurrence at any level is frequent in cases of neurofibromatosis, and iterative surgery might be necessary.

8.4.2.3
Miscellaneous

The most common tumors to seed in the subarachnoid space of the cauda equina are metastasis of PNET (medulloblastoma), ependymoma of the posterior fossa, and germ cell tumors (15 cases). There is no place for surgery in such cases, except to perform the diagnosis in very rare cases of PNET located first at that level. Rare cases of intradural sarcomas and meningiomas can also be encountered (3 cases).

8.4.3
Extradural Tumors

Except for neurofibromas observed in NF1 or NF2, surgery is only palliative and children are operated on for diagnosis or in cases of severe and rapid neurological deterioration. Location of these tumors at the level of the lumbar part of the spine is very rare; also bladder dysfunctions are rare.

Neuroblastomas invading the spinal canal are frequent in infants and young children. They are very sensitive to chemotherapy and surgery is indicated only to remove residue after oncological treatment. They are frequently observed at the level of the thoracolumbar region. The mature form of that tumor (ganglioneuroma) is usually encountered in teenagers (3 cases; Fig. 2).

Bone tumors compressing the conus medullary or the roots, as in Ewing sarcoma, aneurysmal bone cyst, and others, are very rare at the level of lumbar spine.

8.4.4
Dysembryoplastic Tumors

8.4.4.1
Lipomas

Lipoma is the most common type of spinal dysraphism. The diagnosis can be made very early with the presence of a fat mass medial or asymmetrical in the back. Sometimes, a superficial angioma, a dimple, or an appendage may be associated. Sphincter manifestations are very frequent, varying from 50 to 80% in adulthood [5, 30, 33]. The existence of a sacral agenesis increases the risk of sphincter dysfunction. The urodynamic screening, usually normal or subnormal in infants, is frequently disrupted in older children, teenagers, and adults showing a hyperactive bladder and a vesico-sphincter dyssynergia. Several anatomical classifications have been described in the literature, and according to Choux et al. three types are distinguishable (see Table 3) [5]. Complex forms, such as lipomyelomeningocele and lipomyelocystocele, can also be encountered

The natural outcome of spinal lipomas has not been well studied in the literature [16, 30]. If all the authors agree about the interest of prophylactic surgery for lipomas of the filum, controversy develops concerning lipoma of the conus (see Fig. 3). Early surgery is recommended by the vast majority of authors [5, 10, 14, 15, 17, 25, 33, 36], who argue that in asymptomatic patients prophylactic surgery provides some protection for future neurological and urological deterioration, and a strong argument is demonstrated by Dorward et al. [10], where patients operated on before 3 years of age were significantly more normal than patients older than 3 years. The defenders of conservative treatment in asymptomatic patients argue about the similar results for patients operated on or not [16, 30]. It is our policy to operate on routinely infants and young children who are even asymptomatic. Our major argument is that patients operated on, with a neurological bladder, do not recover a normal status despite surgery.

Table 3. Anatomical classification according to Choux et al. [5]

1) Extradural lipoma

2) Intradural lipoma
    a) Lipoma of the filum
    b) Intramedullary lipoma

3) Extra- and intradural lipoma
    a) Dorsal lipoma
    b) Caudal lipoma

8.4.4.2
Dermal Sinus and Dermoid Cysts

Dermal sinus develops from the skin and crosses the subcutaneous layer to enter into the epidural space. It can penetrate the dura to develop a dermoid cyst until the conus medullaris (Fig. 4). In case of rupture, bacterial meningitis can develop and severe neurological deficit, such as paraparesis or paraplegia with urological bladder dysfunction, may complicate the clinical manifestation. Surgery is mandatory in all cases of dermal sinus. The entire tract and the cyst must be removed to avoid that severe complication.

8.4.4.3
Neurenteric Cysts

Neurenteric cyst is very rare, and in a review of the literature, Hirsch and Hirsch in 1989 collected only 29 cases [12]. Neurenteric cysts can be located at any level of the spine, and only 15% are thoracolumbar. They develop mostly anterior to the spinal cord. In our series, four of these cysts were in the lumbar region. Clinical presentation can be progressive or acute, and severe neurological deficit associated with neurogenic bladder has been described. Neurenteric cysts must be totally resected.

8.5
Conclusion

The pathologies described in this chapter represent a great disparity of lesions. The common denominator is the possible similar clinical presentation. The functional prognosis depends on the severity of the clinical manifestations and the final result from precise histological diagnosis.

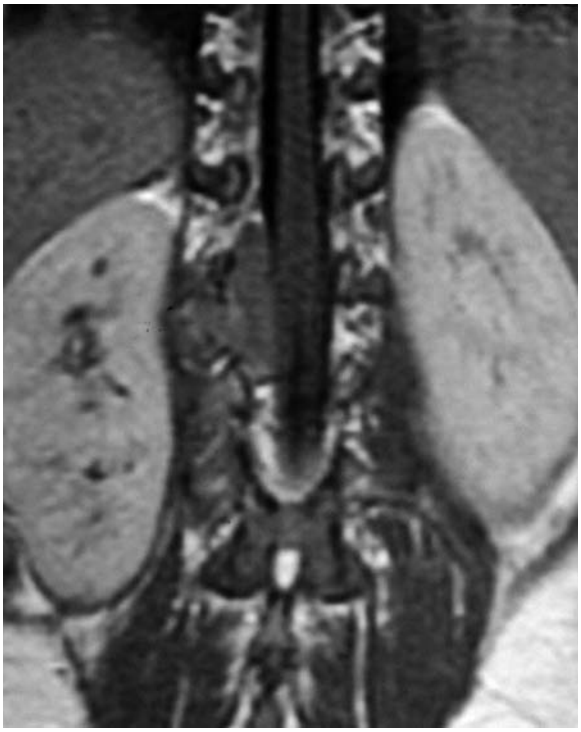

Fig. 2. Ganglioneuroma. Frontal view on T2-weighted image shows an extraspinal mass crossing the foramen to enter the epidural space and compression of the conus at T12–L1 level

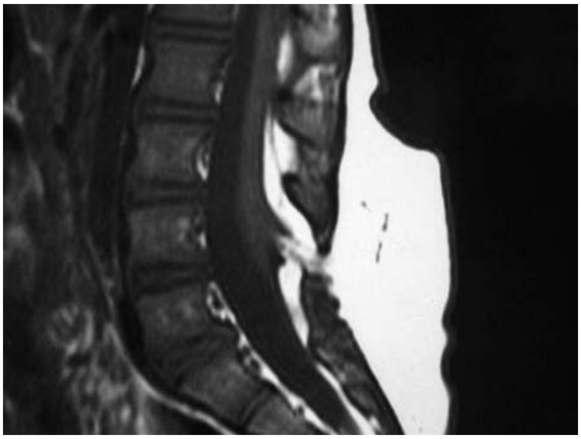

Fig. 3. Lipoma of the conus. Magnetic resonance imaging shows a typical dorsal lipoma extending subcutaneously through the bone defect.

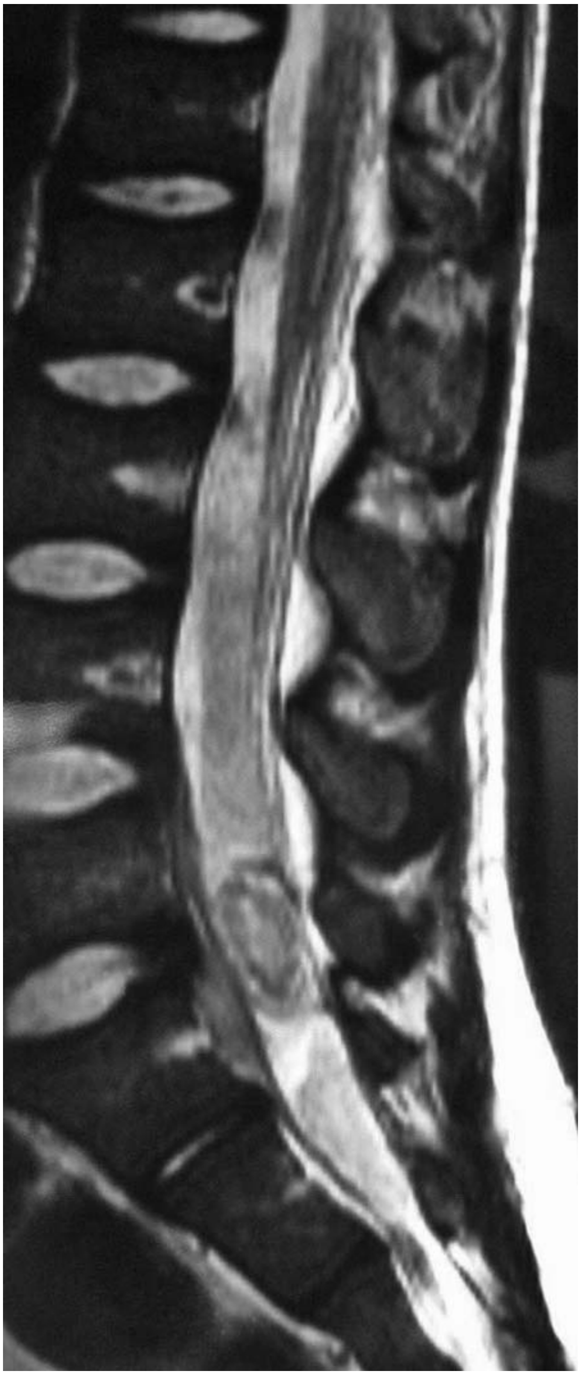

Fig. 4. Huge dermoid cyst which developed in the cauda equina extending from L2 to S1.

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Spinal Cord Injuries and Neurogenic Bladder Dysfunction

9

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9.1
Introduction

Spinal cord injuries (SCI) can affect bladder physiology in different ways. Most classification strategies assume that voiding dysfunctions after an injury of the spinal cord can be predicted based on the site of the neurological lesion [4]. In clinical practice, however, predicting the lesion site and its consequences is usually more complicated [28]. The complex destructive forces may extend tissue damage, so that the variability in voiding characteristics is infinite, especially in injuries that involve lesions around the thoracolumbar vertebra junction [1]. In addition, the intricacy of the cauda equina and pelvic plexus, as well as possible combinations of conal and/or suprasacral injuries, make the neurourological patterns less predictable [4]; however, SCI may also be non-traumatic, as those caused mainly by infectious diseases or tumors.

After SCI, it may take months for some function of the lower urinary tract to be restored, and the degree of functional recovery varies greatly [4, 7]. The pathological changes in bladder function explain the variation in urodynamic findings in this specific group of patients. The neurological examination is usually the first diagnostic test administered to SCI patients; however, little attention has been given to its possible predictive value for the recovery of bladder function [4]; thereafter, an accurate examination of bladder function is fundamental to determine the clinical outcome of these patients and to plan therapeutic strategies and follow-up [28]. The aim of this chapter is to give an overview on SCI and their consequences.

9.2
Etiology and Epidemiology

9.2.1
Traumatic SCI

Traumatic SCI affects over 200,000 people in the United States, with nearly 10,000 new injuries annually [18, 20]. Patients are typically young (average age 25 years), with life expectancies only slightly reduced when compared with the non-SCI population; thus, the medical and functional care decisions can lead to tremendous annual and lifetime costs [20].

Children comprise 2–5% of all patients with spinal cord injuries [10]. Long-term functional outcomes after SCI result from a combination of acute neurological recovery in addition to medical intervention, rehabilitation, and community reintegration [5, 20]. The SCI occurs in an instant and results in immediate changes in sensory and motor functioning as well as in bowel and bladder functioning [18]. In addition to these immediate and direct consequences, SCI may result in the development of several types of secondary complications in the years and decades post-onset [6, 8, 18]. Pressure ulcers and urinary tract infections are perhaps the most frequently investigated secondary conditions, whereas little or no attention has been paid to the risk for injuries that occur subsequent to the initial SCI [16, 18].

Spinal cord injury is not a random event; it occurs most often in teenagers and young men engaged in high-risk activities [17]. Although motor vehicle collisions (MVCs) continue to be the primary cause of SCI, injuries from violence have increased dramatically in recent years, particularly among racial and ethnic minorities [22, 24]. Etiology varies with age. Violence is a more common cause among teenagers and young adults, whereas falls are the more common cause among the elderly [18, 33]. Violence is more common among African-Americans and Hispanics [18].

9.2.2
Non-Traumatic SCI

The diagnosis of nontraumatic SCI is a crucial aspect in the epidemiologic study of this pathology. The spinal cord can be affected by many diseases. Patients with nontraumatic SCI are treated by physicians with different specializations (internal medicine, surgery, physical medicine, and rehabilitation), adding to the difficulty of epidemiological studies [5]. It seems that in the U.S. the annual incidence of nontraumatic SCI is 8 per 100,000 [5, 6]; however, incidence can change greatly in different countries. A Spanish retrospective study based on questionnaires completed at home reported a lower incidence: 0.51 per 100,000 [5, 16]. Another retrospective study, based on data recorded for the entire Fiji population , reported an incidence of 0.87 per 100,000, which is also lower than Kurtzke's findings [1, 5, 22]. Biering-Sørensen et al. reported 92 cases of nontraumatic SCI in 10 years in Denmark (24.3% of the whole case series) but were unable to estimate the actual incidence for lack of information, [2, 5]. In a retrospective Dutch study, Schönherr et al. reported an incidence of 0.16 SCIs per 100,000, 52% of which being nontraumatic [5, 33]. Schönherr also expressed concern that the data may not have been entirely reliable [4, 5]. Data from different case series show significant variability in the rate of traumatic and non-traumatic SCI, due to geographic location, type of care department, physician's diagnostic skills, and people's health expectations [22, 24].

In a long-term observational study (1950–1979) of subjects with nontraumatic SCI, these lesions are reported to account for an increasing proportion of total SCIs (from 15 to 45%) [5, 8]. More recent studies report different findings, from 20 to 52% [16, 18]. As for the etiology of non-traumatic SCI, infectious causes are more frequent in developing countries, whereas neoplastic causes are more frequently reported in the western world. Other etiological factors are represented by inflammatory diseases, vascular disorders, primary neoplastic or osteodegenerative disorders, multiple sclerosis, spinal cord metastasis, degenerative central nervous system diseases, and hereditary or congenital diseases [8, 16].

9.3
Site of Neurological Lesion

Spinal cord injury can disrupt upper- and/or lower-motor and sensitive pathways and results in either a complete or an incomplete lesion. Although recent advances in primary damage healing, rehabilitation, and prevention of complications have improved the prognosis of SCI the consequences are still traumatic and disabling [26]. Lesions at different levels of the spinal cord can affect bladder physiology in different ways. The effects of SCI on the voiding function generally correlate to the neurological level; however, in cases of spinal injury at the junction of the thoracic and lumbar spine, the special anatomic relationship of the spinal cord to the bony spine must be considered [28]. It is generally accepted that the spinal cord terminates at the lower border of the first lumbar vertebra, and that all the lumbar and sacral segments lie between the upper border of the tenth thoracic and the first lumbar spine processes [28, 29]; thus, the twelfth thoracic vertebra usually overlies the fifth lumbar segment of the spinal cord [28, 31]. After SCI, it may take months for some function of the lower urinary tract to be restored, and the degree of functional recovery varies greatly [32]. After an acute spinal cord lesion, hemorrhagic necrosis and edema affect the cord segments adjacent to the SCI. Later changes include gliosis along the degenerated tracts, which normally connect the sacral cord with the brain [19, 28]. Some patients with complete lesions above the level of the sacral cord may have evidence of trauma or infarction of the lumbosacral cord. Such patients will show flaccid bladder and little sphincter tone similar to those observed after a lesion at the conus level [26, 28]. These pathological changes explain the variation in urodynamic findings of this specific group of paraplegic patients. The changes are well delineated by the Bors and Comarr classification [3] of neurogenic bladder dysfunction, which enables one to distinguish between lower urinary tract dysfunction and upper motoneuron, lower motoneuron, or mixed lesion types, and between complete and incomplete lesions according to the extent of the neuronal involvement (Table 1) [20, 26, 28]. The need to predict outcome on the basis of expected neurological recovery and associated functional recovery has been emphasized as essential for health care planning. This knowledge makes it possible to answer questions regarding function, which patients usually ask after SCI: “Will I walk again?” and “What will I be able to do?” Furthermore, in countries with health care systems based on insurance, rehabilitation professionals have to justify and advocate for appropriate services; thus, predicting recovery has become a rehabilitative imperative [26].

Table 1. Bors and Comarr classification of bladder dysfunction. (From [35])

Sensory motor lesion	Mixed lesion
Upper motoneuron lesion	Upper somatomotor neuron
Complete/incomplete	Lower visceromotor neuron
Balanced/inbalanced	Lower somatomotor neuron
Lower motoneuron lesion	Upper visceromotor neuron
Complete/incomplete	Normal somatomotor neuron
Balanced/inbalanced	Lower visceromotor neuron

9.4
Examination

In general, SCI patients are hospitalized the same day of the injury in an emergency center but are admitted to specialized rehabilitation centers only some weeks or months after the injury occurred. Here, the patients are accurately studied and a rehabilitation plan is scheduled. Patient information is collected according to standard Model Spinal Cord Injury Systems (MSCIS) procedures at four time intervals: (a) admission to acute care; (b) admission to inpatient rehabilitation; (c) discharge from inpatient rehabilitation; and (d) 1 year post-injury (follow-up) [20].

The fractures of the spine are verified radiologically, by radiography, computer tomography, and/or magnetic resonance imaging. Patients are assessed neurologically on the day of admission according to the American Spinal Injury Association (ASIA) protocol [4, 20]. Special attention is given to the ASIA sensory scores.

To evaluate more specifically the value of the ASIA protocol in predicting bladder recovery, a sacral sensory ASIA score is defined and recorded for each patient. The score is defined as the sensory impairment of the S2–S5 dermatomes according the ASIA protocol. Additionally, the bulbocavernosus reflex (BCR) and the voluntary contraction of the external anal sphincter are tested clinically in all patients [4, 20, 28].

To exclude the presence of peripheral neuropathies, all patients are electrophysiologically examined by means of nerve conduction studies of peroneal, tibial, and sural nerves of both legs, and needle electromyography of the paraspinal muscles, gluteus maximus, gluteus medius, adductor longus, vastus medialis, tibialis anterior, gastrocnemius, and the anal sphincter bilaterally [4, 28, 29]. Urodynamic examination is performed at least once during hospitalization. Drugs that could interfere with the urethrovesical function are discontinued at least 48 h before the examination.

9.5
Classification

The international standards for neurological classification of SCI has become established as the primary neurological description for traumatic SCI. The standards were initially developed by the American Spinal Injury Association (ASIA) to classify neurological deficit after SCI, and have since come to be used as an outcome measure [5]. Accordingly, a spinal cord lesion is classified as complete or incomplete. Incomplete is defined as the presence of any sensory or motor function in the lowest sacral segments [29].

The American Spinal Injury Association (ASIA) motor index total score is calculated for each patient with a SCI [29]. Scores ranging from 0 to 100 are assigned at the time of acute care admission, at admission, and at discharge from inpatient rehabilitation, and at 1-year follow-up [2, 20]. ASIA motor index change scores are calculated according to Model Spinal Cord Injury System (MSCIS) evaluation between initial admission and rehabilitation discharge and between rehabilitation discharge and 1-year follow- up. The ASIA motor index efficiency scores are calculated by dividing the ASIA motor index change scores by the number of days.

The ASIA Impairment Scale (AIS) is assessed according to MSCIS at admission (for patients admitted on day of injury), at discharge from inpatient rehabilitation, and 1 year after the injury [2, 12, 20]. For the pur-

Table 2. Asia Impairment Scale

Grade				
A	B	C	D	E
Complete	Incomplete	Incomplete	Incomplete	Normal
No motor or sensory functionis preserved in the sacral segments S4–S5	Sensory, but not motor, function is preserved below the neurological level and includes the sacral segments S4–S5	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade <3	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of ≥3	Motor and sensory function are normal

pose of the analysis, AIS injury level categories generally are recoded into numeric format to allow change scores to be computed [e.g., grade A (complete) into 0; grade B (sensory only) into 1; grade C (motor, not functional) into 2; grade D (motor, functional) into 3; grade E (normal) into 4]; therefore, a change score of 1 could represent the change from an AIS grade A to an AIS grade B, or the change from an AIS grade D to normal functioning (grade E; (Table 2) [12, 13, 20].

In general, these classification include several variables such as: single neurological level; sensory level, right and left; motor level, right and left; the ASIA Impairment Scale (AIS); light touch score; pinprick score; motor score; and, for individuals with complete injuries, extent of sensory and motor zone of partial preservation, right and left [5, 29]. The ASIA motor scores have been most often used in describing recovery after SCI or response to interventions. At times, motor recovery has been reported by subgroups based on AIS grade, such as complete (AIS grade A) vs incomplete (AIS grades B, C, and D), or by level of injury (tetraplegia or paraplegia) [5, 20].

Recent evaluations of the ASIA motor score suggest that it is not unidimensional. Factor analysis indicates that the ASIA motor score actually consists of two subscales, an upper-extremity motor score (UEMS) and a lower-extremity motor score (LEMS), each consisting of the respective ten key muscles. Separating the ASIA motor score into these two scales extracts more information from the data, and has been shown to better predict changes in self-care and mobility during rehabilitation than the use of a single motor score [2, 5, 20].

9.6
The Role of Experimental Models

Spinal cord injury rostral to the lumbosacral level causes urinary bladder dysfunction characterized by hyperreflexia and incontinence. In SCI patients, uncoordinated bladder and external urethral sphincter activity, termed detrusor–sphincter dyssynergia (DSD), can increase outlet resistance and induce high intravesical pressures during voiding that can damage the upper urinary tract [4]. To solve this problem, in the past few years, several experimental studies have been performed to search for an adequate therapy for patients with SCI and bladder dysfunction. Research lines developed in recent years are based mainly on two issues: pharmacological therapy and surgical therapy creating experimental models [30].

An ideal therapy for lower urinary tract dysfunction in SCI patients would be one that reduces detrusor hyperreflexia and thereby promotes urine storage at low intravesical pressures and promotes efficient voiding at low pressures by reducing DSD. The results of some studies on SCI rats indicate that some of these effects can be produced by administering NMDA (MK-801) and AMPA (LY215490) glutamatergic receptor antagonists. Administration of the antagonists individually or in combination increased VT for inducing micturition (i.e., increased functional bladder capacity) and reduced voiding pressure [25, 35].

Other studies based on experimental models in rats have determined that bilateral section of the hypogastric nerves (HGN), which provide the major sympathetic input to the urinary bladder neck/proximal urethra, improve voiding by reducing urethral resistance in conscious, female SCI rats 2–3 weeks after T7–T9 transection of the spinal cord [34, 35].

The results show that elimination of the hypogastric nerves decreases maximal voiding pressure and improves voiding efficiency, indicating that sympathetic pathways are involved in the abnormal voiding in SCI rats [34, 35].

The rapid development in neural regeneration of combining trophic factors with microsurgical techniques has new implications for the treatment of thoracolumbar spinal injuries. In recent laboratory studies, paraplegic rats underwent the full repair strategy (white-to-gray bridges, fibrin glue with acidic fibroblast growth factor, compressive wiring), which resulted in the return of hind limb positioning and movements and partial weight bearing [4, 19].

Although these studies have given interesting results, they suggest that more research should be conducted in the SCI rat models to evaluate the influence on voiding function of adrenergic-blocking agents and other treatments directed at reducing urethral outlet resistance [4, 34].

9.7
Surgical Management of Patients with SCI

Surgical spine intervention after traumatic SCI typically involves vertebral stabilization and/or decompression of neural tissue. Although the past few decades have seen much advances in spinal surgical techniques and an increase in spinal surgeries after SCI, controversy still exists regarding the potential neurological benefits and timing of the surgery. Traumatic SCI affects over 200,000 people in the U.S., with nearly 10,000 new injuries annually [20]. People are typically young (average age 25 years), with life expectancies only slightly reduced when compared with the non-SCI population; thus, the medical and functional care decisions can lead to tremendous annual and lifetime costs [9, 20].

Long-term functional outcomes after SCI result from a combination of acute neurological recovery in addition to medical intervention, rehabilitation, and community reintegration. Early interventions focus on treatment to enhancing neurological potential after acute SCI. In the early 1990s, the National Acute Spinal Cord Injury Study (NASCIS-II) concluded that the administration of methylprednisolone within the first 8 h (30 mg/kg bolus and 5.4 mg/kg hourly for 23 h) after traumatic non-penetrating SCI may enhance the potential for neurological improvement, thus indicating the potential of early intervention on secondary SCI [9, 20, 21]. The NASCIS-III study further revealed significant improvement in motor scores on those with methylprednisolone and tirilazad started 3–8 h after injury. Because these findings have not been consistently replicated, recommendations have not been universally adopted [20, 21].

Criticism of the NASCIS studies has been expressed that their data were not compelling, that use of the data remains experimental, and that clinicians should adhere to strict inclusion criteria when considering its use [21]. Research with animal models has provided evidence that early decompressive surgery could lead to improved neurological recovery after SCI, further suggesting the importance of early intervention. The number of human spinal surgical studies using prospective, randomized, or controlled methodologies is limited [19, 26]. The current literature available has shown varying results, some indicating the potential neurological benefit associated with "early" spinal decompression and others not.

Although uncertainties remain as to the potential neurological benefits or optimal timing of surgical intervention after SCI, increased medical complications have not been reported. Schlegel et al. reported fewer medical complications in patients who underwent decompressive surgery less than 72 h after injury compared with those who had surgical treatment after 72 h [9, 19, 26]. Nonetheless, spinal surgical procedures carry risks such as neurological deterioration, bleeding, infection, and dysphagia. Additionally, several studies have noted the beneficial effects of surgical intervention for earlier patient mobilization, which contributes to earlier transition to rehabilitation, shorter hospital length of stay (LOS), and decreased hospital costs. Decreased LOS is associated with decreased medical morbidity [20].

9.8
Clinical Outcome and Follow-up

Spinal cord injury can disrupt upper- and/or lower-motor and sensitive pathways and results in either a complete or an incomplete lesion. Although recent advances in primary damage healing, rehabilitation, and prevention of complications have improved the prognosis of SCI, the consequences are still traumatic and disabling [26]. Analyzing the international literature it seems that the need for surgery and the outcome could be related to the etiology of injury. Spinal surgery after SCI is not uncommon and is usually performed secondary to vertebral instability or in the presence of neurological decline [20]. The controversy remains as to whether spinal surgery after SCI leads to additional benefits in the areas of neurological and functional outcome. In fact, it has not been demonstrated whether immediate decompression is better than non-surgical intervention (and immobilization with an orthosis) to provide adequate stabilization and improve outcomes [10, 11]. Fixation for stabilization is important if a patient has an unstable spine.

Patients with motor vehicle collision (MVC) etiologies are more likely to undergo early surgical intervention [20]. This may reflect the mechanism and increased force of injury associated with MVC-induced SCI, thus increasing the likelihood of unstable vertebral fractures. Subjects with SCI secondary to falls, sports, or medical and surgical complications may be less likely to have vertebral fractures or vertebral instability [14, 20]. McKinley et al. report that no significant differences in changes of neurological status were noted between early and late surgical and non-surgical groups, either for neurological level of injury or ASIA motor changes [19, 20]; thus, this study did not reveal neurological benefits associated with early or late vertebral surgical intervention as compared with those who did not undergo surgery. Acute care and total LOS were longer in the late-surgery group [20]. Earlier surgery may promote earlier patient mobilization, transition to rehabilitation, and, subsequently, earlier discharge to community. Patients within the late surgical group also had higher acute care and total hospitalization charges. Pulmonary complications, such as pneumonia and atelectasis, appear to have occurred more frequently in those with late surgical intervention [15, 19, 20].

As for neurological recovery, Scivoletto et al. report an incidence of neurological recovery in 27% of the patients [26]. The issue of pharmacological treatment in the acute phase of SCI is still a matter of debate, even if methylprednisolone seems to improve neurological recovery [21, 23].

The ASIA impairment designation seems to have prognostic value; however, recovery from complete lesions is quite limited. Despite recent advances in treatment and rehabilitation, patients who remain ASIA class A at 1 month after a spinal cord lesion have little or no expectation of recovery [2, 26, 27]. Patients with ASIA class-B impairment at admission have a significantly better prognosis than ASIA class-A patients: about half the patients change their impairment grade, and, what is more noteworthy for rehabilitation professionals, 25% regain functional status [2, 5, 26]. This finding reflects the importance of sensory preservation for neurological recovery; thus, the absence of any motor function in patients with SCI (but with sensory preservation) is not an absolute indicator of poor motor recovery [20, 26]. In some studies, patients with ASIA class-C injury at admission had the best neurological improvement both in terms of ASIA grade improvement (more than half the patients regained functional status) and motor score increase [2, 21]. Finally, patients with ASIA class-D injury were subject to a ceiling effect (i.e., they did not have much to improve) and had lower ASIA grade improvement frequency and lower motor score increase [11, 20]. It was recently reported that a great deal of the recovery in patients with SCI occurs within 2 months of injury; thus, it is possible that, by the time patients are admitted to hospital, part of the recovery has already taken place. The timing of the first examination is still a matter of debate. Several articles suggest that an examination 72 h or 1 week after injury is the best prognostic indicator for neurological recovery. Early examination is also needed in countries where a prognosis must be obtained within the first weeks for financial (insurance) reasons [20, 27]. For outcome evaluation, four variable expressions of injury characteristics are important: neurological level of injury (paraplegia, tetraplegia), ASIA impairment classification (classes A, B, C, D), time from lesion (<40 days, >40 days), and/or age categories [10, 20, 26].

Lesion etiology does not seem to influence neurological recovery. McKinley et al. showed that patients with traumatic and non-traumatic injuries have comparable outcomes [19, 20].

9.9
Long-Term Urological Outcomes

As for neurological bladder dysfunctions, SCI is commonly associated with neurogenic lower urinary tract dysfunction. Compared with the general population, the incidence of long-term indwelling catheterization, recurrent urinary tract infections (UTIs), and bladder stones is elevated in patients with SCI [19, 20, 26].

Historically, bladder management has consisted primarily of reflex voiding or chronic indwelling catheterization. The long-term urological complications in adults following SCI have been well documented. Renal disease is the leading cause of death in adults with SCI. Early pediatric SCI studies revealed upper tract changes in 31–43% of patients [4, 10]; however, these cases were commonly managed with reflex voiding and the use of anticholinergics was infrequent.

Complications, such as infections, hydronephrosis, vesicoureteral reflux, and renal scarring, were found in many children [8].

Early studies of urological outcomes in patients with SCI derive from groups of veterans examined during World War II and Korean War with 25- and 20-year follow-up, respectively [10, 22]. Patients were thought to have balanced bladders if they did not have reflux, had residual urine less than one-third bladder capacity, and did not require an indwelling catheter. An unbalanced bladder required an indwelling catheter for any reason. Renal disease accounted for 43% of deaths in these series [10, 22]. The patients with unbalanced bladders had a higher incidence of upper tract complications and mortality rates than those with balanced bladders [4, 10]. After the introduction of clean intermittent catheterization (CIC) by Lapides et al., bladder management evolved away from reflex voiding and indwelling catheters to the widespread use of urodynamics, CIC and anticholinergic medications [8, 10]. Urodynamics has elucidated high voiding pressures and DSD in patients previously thought to have balanced bladders [12, 22]. A study of 140 patients with SCI showed similar rates of upper tract deterioration in those with areflexic and hyperreflexic bladders (17.5 and 16%, respectively) [4, 8, 10]. On the other hand, comparison of storage and voiding pressures between patients with upper tract changes and those with normal upper tracts was revealing. Patients with upper tract deterioration had average storage pressures of 58 cm water and average maximum voiding pressures of 115 cm water compared with 24 cm water and 72 cm water, respectively, for patients with preserved upper tracts [4, 8, 10, 12]. In a series of 85 adults with SCI treated with sterile intermittent catheterization, 33% exhibited reflux or upper tract changes on excretory urogram [10]. Increasing the frequency of catheterization from two to three times per day to six times daily eliminated reflux or hydronephrotic changes [4, 10]. A study of 254 patients with SCI examined bladder compliance and demonstrated a dramatic association between low compliance and hydronephrosis. Low compliance was defined as pressure of 5 cm water or greater at 100 cc [10, 12]. The incidence of hydronephrosis was 64% and vesicoureteral reflux 46% in patients with low compliance, compared with 21 and 6%, respectively, in patients with normal compliance [12]. Few studies have examined young patients with SCI. Of 18 children with SCI studied by Fanciullacci et al, 15 underwent videourodynamic (UDS) studies [8]. Of these patients, 12 had hyperreflexia and 3 had areflexia [8]. Only 2 patients were treated with intermittent catheterization and oxybutynin; the remainder were considered to have recovered balanced bladder function. No patient was continent. At a long-term follow-up renal deterioration was observed in 6 of 14 patients [8].

Chao and Mayo retrospectively evaluated 40 children with SCI with a mean age of 9 years at time of injury [4]. Of the patients, 28 had longer than 1-year follow-up. Patients with trabeculated bladders, DSD, or detrusor pressures >40 cm water were placed on CIC and anticholinergic medication. At follow-up 11 patients were reflex voiding and 17 were using CIC [4]. On fluoroscopy 43% of the patients had smooth bladders and 57% had trabeculated bladders [4]. No upper tract deterioration was observed and no augmentations were performed. Bladder capacity in injured infants appeared to increase with time but to decrease in older children.

Generao et al. reported improved continence and decreased rates of infection with the institution of CIC and anticholinergic medication. In this series many patients who were initially wet and had frequent infections become damp or dry and infection-free [10]. This author documented through serial UDS that in the majority of pediatric bladders grow following SCI, and in the few children who displayed decreasing capacity with time, it was not clear that non-compliance with CIC was the underlying cause [10].

9.10
Conclusion

Spinal cord injury seems to have increased in recent years, above all those due to MCV, and very frequently involves children and teenagers. The ASIA impairment designations have prognostic value. Recovery from complete lesions is limited. Patients with ASIA class-B impairment at admission have a better prognosis than those with ASIA class A [20]. Patients with ASIA class C at admission seem to have the best neurological improvement [2, 19]. Finally, ASIA class-D patients have lower ASIA grade improvement [26]. Neurological recovery seems to be negatively associated with patient age and delayed rehabilitation, but not with other lesion features. With regard to treatment in the acute phase of the lesion, no definitive statement can be drawn from analyzing the literature. The issue of pharmacological treatment in the acute phase of SCI is still a matter of debate. High-dose methylprednisolone seems to improve neurological recovery, but recent evidence based on analysis of these results indicates that this therapy should not be recommended [27]. The role of surgery is also unclear. It seems that surgery plays a role in case of vertebral instability, and early surgery is preferable to late surgery in terms of results, hospital stay, and complications.

Data on the effect of age on SCI patient outcomes have been reported in several studies, and it seems that young patients appear to do better than older ones [26]. This difference seems to be in relation with the different efficiency of spinal cord recovery in children and adults. A good and long-term rehabilitation plan is essential [20]. As for the urological treatment, the strategies of patients with SCI have been modified. The prevention of long-term indwelling catheterization is one of the most important goals in the treatment of patients with SCI, and presently clean or aseptic intermittent catheterization with single-use catheters in association with pharmacological therapy is regarded the treatment of choice [20].

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Neurogenic Bladder and Anorectal Malformations

10

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10.1
Introduction

Neurogenic bladder is expected to occur in a significant number of patients who are born with anorectal malformations, mainly for two reasons:

1. The overwhelming majority of cases have the rectum in a fistulous communication with the genitourinary tract. The repair of the malformation, in the great majority of cases, requires, as a mandatory step, to separate the rectum from those structures, with the consequent risk of injury to the genitourinary structures, or the nerves that innervate them.
2. Anorectal malformation cases also have a tendency to suffer from different congenital defects of the spinal cord. These defects include hemivertebra, a defect called tethered cord, different degrees of sacral anomalies, and myelomeningocele. All degrees of these spinal cord anomalies may occur, and therefore the degree of neurological deficit affecting the bladder in these patients may be represented by a spectrum of dysfunctions of the urinary tract; therefore, we believe it is important to discuss the problem of neurogenic bladder and anorectal malformations in two different categories, as well as to separate males from females into the following groups: (a) patients without spinal cord anomalies; and (b) patients with spinal cord anomalies.

10.2
Neurogenic Bladder in Patients with Anorectal Malformations Without Spinal Cord Anomalies

10.2.1
Male Patients

It is extremely unusual to see male patients – with anorectal malformations, as well as normal spine and cord, who underwent a technically correct operation to repair their defect – suffering from neurogenic bladder. The only cases that we have seen are those patients who suffered some sort of nerve damage during an attempted, usually failed, repair of an anorectal malformation [1]. From a series of approximately 800 male cases surgically treated by us to repair an anorectal malformation, using the posterior sagittal approach, we have seen two patients that had urinary retention after the Foley catheter was removed, but both of them had significant sacral deficiencies. If we exclude the patients with severe sacral and spinal abnormalities, in our series there has never been a case of a neurogenic bladder. Even in those patients who suffered from urinary retention, it turned out to be a temporary problem, and subsequently, they behaved like normal patients from the urinary point of view and they have urinary control. We must assume that the operation itself (posterior sagittal anorectoplasty), even when performed in a meticulous manner, may have some sort of temporary or permanent effect on the innervation of the bladder. Perhaps those changes could be demonstrated by very precise urodynamic studies. Those studies have been done [2], but they indicate that there is no real damage consecutive to the posterior sagittal approach of these patients when the operation is performed meticulously. Simultaneously, we had the opportunity to retrospectively analyze 500 cases that were surgically treated at other institutions and came to our hospital looking for help because they suffered from fecal, and sometimes urinary, incontinence. We were surprised to find that 26% of the patients suffered from different degrees of neurogenic bladder that could be attributed to the surgical exploration [1]. Further analysis of the possible cause of this neurological damage showed that the most common scenario in which this occurred was when the surgeon did not perform a good preoperative high-pressure distal colostogram or else performed the study, but it was not done correctly. As a consequence, the surgeon decided to operate posterior sagittally without having knowing the precise location of the rectum. The result of this was an exploration in the search for the rectum in an extremely delicate area, which is the posterior aspect of the urethra. As a consequence, these patients frequently suffered from injuries to the posterior urethra, vas deferens, prostate, bladder neck, and nerve erigenti. The parents often noticed that the baby had erections before the procedure and they never saw an erection again after the operation. Three patients suffered from a complete division of the posterior urethra and two patients actually underwent a pull-through of the bladder because the surgeon thought that it was the rectum. These patients suffered from permanent, severe neurogenic bladder [1]. Many of these patients with neurogenic bladder were subjected to vesicostomies, and eventually they required a bladder augmentation and some sort of continent diversion (Mitrofanoff). These problems are potentially preventable.

All repairs of male patients with anorectal malformations must be done only when the surgeon knows the exact the type of malformation. Most of these cases of neurogenic bladder occurred in patients who had the rectum connected to the urinary tract, very high into the area of the prostatic urethra or the bladder neck. The surgeons did not know this; however, they approached the patients posterior sagittally and encountered the urinary tract rather than the rectum. A good distal colostogram should prevent this from happening.

In a case of rectobladder neck fistula one should never look for the rectum posterior sagittally because it will not be found. The rectum should be looked for through the abdomen (with laparotomy or laparoscopy). The incision from below is made only to facilitate the pull-through of the rectum, but not to look for the rectum. The rule of remaining exactly in the midline during the posterior sagittal operation cannot be overemphasized. We believe that not respecting that rule is another potential source of damage to the nerves. The nerves that provide innervation to the bladder neck and the corpora come from the anterior orifices of the sacrum and run on both sides of the midline. When the rectum is located high in the pelvis, these nerves run closer together in the midline and that is why it is very important to remain in the midline during these operations.

10.2.2
Female Patients

When discussing neurogenic bladder in female patients with anorectal malformations, it is necessary to consider two categories: (a) anorectal malformations other than cloaca; and (b) cloaca.

10.2.2.1
Non-Cloaca Patients

Non-cloaca patients with normal spine and cord should not suffer from neurogenic bladder. In approximately 400 cases of non-cloaca female patients with a normal spinal cord operated by us, we have never seen a case of neurogenic bladder. In fact, even patients with significant degrees of sacral deficiencies do not have neurogenic bladder. We feel that even when most likely a urodynamic study may show some abnormalities, clinically these patients behave like children with normal urinary control. Patients within this group, suffering from neurogenic bladder may, therefore have an iatrogenic cause.

10.2.2.2
Cloaca Patients

Cloaca patients, on the other hand, represent a completely different spectrum of problems. The spectrum varies according to the length of the common channel. Cloaca is a defect in which rectum, vagina, and urethra come together to form a common channel that opens into a single orifice at the place where the normal urethra opens. Interestingly, the length of the common channel determines the degree of urinary malfunction that these patients have [3]. We have seen, for instance, that when babies are born with a common channel <3 cm long and the cloacal defect is repaired posterior sagittally, 20% of them require intermittent catheterization to empty their bladder. On the other hand, when the common channel is longer than 3 cm, 80% of these patients require intermittent catheterization to empty the bladder [3]; however, the bladder malfunction seen in patients with cloaca is very different than the one seen, for instance, in spina bifida and/or meningocele patients. In patients with cloacas we do not see hypertonic, trabeculated, and "Christmas-tree" type of bladders. We see instead only smooth, floppy, hypotonic, large bladders. Also, most of these patients have a competent bladder neck. The combination of a very efficient bladder neck with a smooth, hypotonic large bladder makes these patients ideal candidates for an intermittent catheterization program. The fact that they have a large reservoir with low tone allows them to remain completely dry for several hours between catheterizations.

There are two exceptions to the rule of large bladder and good bladder neck. The first exception includes those patients who are born with separated pubic bones. We believe that those patients are part of the cloacal extrophy spectrum. Those patients are born without a bladder neck. When we inspect their external genitalia we see a single perineal orifice, but it turns out that the orifice is very large. In addition, it becomes obvious that the patient is leaking urine constantly. This allows us to suspect that the patient has no bladder neck. A plain radiograph film shows the separated pubic bones, which confirms the diagnosis. It is important to make this diagnosis, because these patients suffer not only from an absent bladder neck, but also they have a small bladder because it was never distended in utero. In addition, some of them also suffer from other stigmata that are seen in cloacal extrophy cases, such as different degrees of short colon that are important for the final functional prognosis for bowel control.

The other exception to this rule is the group of patients with cloacas born with a very long common channel. They usually have two little hemi-vaginas attached to the bladder neck, or even above the bladder neck. The rectum also connects into the bladder neck. In addition, sometimes the ureters are ectopically located and connected to the bladder neck. During the operation to repair this type of malformation, one has to go into the abdomen, open the bladder, separate the little hemi-vaginas, and separate the rectum and sometimes the ureters from the bladder, which leaves the patient basically with no bladder neck. We feel that these patients do better by closing what was meant to be the bladder neck. Eventually, they will be candidates for complex urinary reconstructions generically know as “continent diversion” (consisting usually of a bladder augmentation and the creation of a conduit that connects the neo-bladder to the abdominal wall.)

It remains to be investigated why patients with cloacas suffer from a lack of contractility of the bladder and different degrees of incapacity to empty the bladder. When they cannot empty at all, they require intermittent catheterization; otherwise, they behave like they are urinary incontinent because they leak urine constantly when the bladder is full. Once we empty the bladder with a catheter, they remain completely dry for several hours. It is not clear whether these bladder motility abnormalities are congenital or due to the repair of these malformations.

At the beginning of our series (the first 180 cases) we were repairing cloacas posterior sagittally, separating the rectum from the urogenital tract and finally separating the vagina from the urinary tract. We then reconstructed what used to be the common channel as a neourethra, and then pulled the vagina down to be placed behind the urethra and then the rectum behind the vagina. With that type of operation, 10% of our patients suffered from urethrovaginal fistulas, and therefore we abandoned that approach. The separation of the vagina from the urinary tract requires a very significant dissection of the urinary tract in a crucial area of the bladder neck, and trigone; therefore, we introduced a maneuver called “total urogenital mobilization” [4], which has been utilized in the last 180 cases. With this maneuver, we separate the rectum from the urogenital tract and pull it down first, and then, rather than separating the vagina from the urinary tract, we mobilize vagina and urethra together as a unit, trying not to interfere with the blood supply. We assume that the nerves run in the same location as the vessels.

When we performed the first total urogenital mobilizations, we saw some patients leaking urine in the following days and we were concerned about the damage that we were producing to the innervation of these structures; however, those patients recovered very well. The early cystographic image demonstrated that the leaking that some of them suffered from postoperatively was probably due to the fact that we are stretching the urogenital sinus, which makes the closure of the bladder neck difficult. Now, we are under the impression that the results, in terms of urinary function, are better in patients subjected to total urogenital mobilization as compared with the previous approaches.

10.3
Neurogenic Bladder in Patients with Anorectal Malformations, Associated with Spinal Cord Deficiencies

10.3.1
Spinal Deficiencies

A significant number of patients with anorectal malformations suffer from hemivertebra. We know that having a hemivertebra has some negative influence in the final functional prognosis for bowel control in these patients. We assume that it may also have some influence on the urinary function; however, the presence of hemivertebra by itself does not explain an obvious neurogenic bladder. In fact, patients with hemivertebra that receive a good operation do not suffer from neurogenic bladder. We believe that they may have some degree of minor functional disturbance, but clinically these are not noticeable.

10.3.2
Tethered Cord

Tethered cord occurs in 25% of all patients with anorectal malformations, according to our series [5]. We do not know the precise impact of tethered cord on the function of the bladder. Obviously, when the patients have very severe deficiencies, including absent sacrum, meningoceles, and tethered cord, they also have a neurogenic bladder. A few patients have good sacrum, good lumbar spine, a “good malformation” and tethered cord, and yet, many of them do not suffer from neurogenic bladder. Some neurosurgeons base the indication for untethering the cord on the results of the urodynamic studies. We do not understand this rationale. On the other hand, we have seen four patients who suffered from neurogenic bladder following the untethering of the cord. We believe that tethered cord and its implications for urine and bowel control are still very controversial, and look forward to more comprehensive prospective studies that will help to clarify the real consequences, implications, and possible therapy for patients with tethered cord and anorectal anomalies.

Most of the experience of neurosurgeons in tethered cord comes from patients with spina bifida and myelomeningocele. The overwhelming majority of patients with anorectal malformations and tethered cord do not have a myelomeningocele. Neurosurgeons frequently extrapolate their experience in the management of patients with tethered cord associated with myelomeningocele into patients with anorectal malformations; however, most of the patients that have tethered cord and anorectal malformations also have other serious defects that can explain the problem of fecal and urinary incontinence, by itself, without the need to look for an explanation by the tethered cord.

10.3.3
Sacral Anomalies

Patients with anorectal malformations suffer from a spectrum of sacral deficiencies that go from an absent sacrum to a completely normal sacrum. When a patient has an absent sacrum, the chances of having bowel or urinary control are zero. When patients have a normal sacrum, they should have normal urinary control. They also have a good chance of having bowel control, although there is no guarantee.

Traditionally, the sacrum was evaluated by counting the number of vertebrae. We used to say that more than three missing vertebrae will result in fecal and urinary incontinence, which is not 100% true. On the other hand, we have seen many patients who have a normal number of vertebrae and yet a very abnormal short sacrum with obvious associated nerve deficiencies; therefore, we decided to look for better parameters to evaluate the characteristics of the sacrum. We came up with a sacral ratio [6]. We have never seen a patient with bowel control with a sacral ratio less than 0.4. Urinary control, surprisingly, is present in some patients with a very deficient sacrum, provided they receive a good operation to repair the anorectal malformation.

10.3.4
Myelomeningocele

A few patients in our series suffer from anorectal malformation and myelomeningocele. These patients all have the same problems seen in patients with myelomeningocele without anorectal malformation. We will not expand on that because the type of neurogenic bladder that these patients have, as well as the treatment and problems that result, are not different in patients with anorectal malformations and those with meningocele without anorectal malformation.

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Neurogenic Bladder in Infections of the Nervous System

11

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11.1
Introduction

The bladder control requires integrated function of cerebral cortex, brainstem, spinal cord, and peripheral nerves. Various infections of the nervous system can affect these levels in isolation or in various permutations and combinations resulting in neurogenic bladder. Viruses such as herpes I, II, and herpes zoster can result in neurogenic bladder due to involvement of frontal lobe in herpes simplex encephalitis by HSV I and cauda equina in HSV II and herpes zoster. AIDS produces bladder involvement as a result of HIV myelopathy or due to various opportunistic infections and tumors. Tropical spastic paraplegia results in progressive myelopathy and micturition disturbances occur in 60% patients. Amongst the bacterial infections, pyogenic meningitis producing spinal cord dysfunctions, epidural abscess, and strategically located frontal lobe brain abscess can result in neurogenic bladder. Spinal tuberculosis produces various types of micturition disturbances due to Pott’s spine, arachnoiditis, granuloma, and vasculitis. In Pott’s spine bladder involvement is associated with severe paraplegia. Two important parasitic diseases, schistosomiasis and cysticercosis, may result in bladder dysfunction because of myelopathy. Lyme disease produces encephalomyelitis and tabes doraslis sensory deafferentation; the later typically results in insensitive bladder. Besides direct infection, a number of viral, bacterial, and triggering events result in autoimmune process leading to a spectrum of parainfectious demyelinating diseases, which include acute disseminated encephalomyelitis, acute transverse myelitis, and Guillain-Barre (GB) syndrome. In transverse myelitis bladder involvement is integral diagnostic feature, whereas in GB syndrome it occurs transiently in some patients. There is paucity of studies on urodynamic changes in various infections resulting in neurogenic bladder. In the acute stage due to shock (cerebral or spinal) there may be areflexic or hypocontractile bladder, and later detrusor hyperreflexia with or without sphincter dyssynergia may develop depending on severity, extent, and level of neurological damage. In general, with the recovery of infection, the bladder functions also tend to recover. In acute transverse myelitis and schistosomiasis, however, there may be persistent bladder dysfunction in spite of full neurological recovery. In the central nervous system (CNS) infective disorders the management of bladder should get due attention. In the acute stage, control of infection and catheterization should be done. The persistent bladder symptoms are managed like any other neurogenic bladder.

Infections of the nervous system are prevalent globally. Various bacterial, fungal, viral, and parasitic infestations affect different parts of the central and peripheral nervous system and thereby result in neurogenic bladder. Different geographical areas, timing of the years, and host factors such as immunological disorders and immunosuppression, increase the susceptibility to infection. Infectious disorders can result in micturition disturbances because of involvement of different regions of nervous system such as cerebral cortex, brainstem, spinal cord, nerve roots and peripheral nerves. Besides the direct involvement of the nervous system, parainfectious events also result in demyelination of nervous system by immune mechanisms in which the organism cannot be detected in CNS. Direct infection of urethra and urinary bladder by various pathogens can also result in micturition disturbances. The majority of the infections are monophasic, which tend to regress or stabilize in due course. The infection resulting in neurogenic bladder may modify the bladder symptoms because of neuronal plasticity. It is important to diagnose the nature and extent of infection so that timely treatment can be provided to prevent mortality and morbidity.

In this chapter, the bladder disturbances due to nervous system involvement at different levels are briefly described, and also some important infections which result in neurogenic bladder are discussed.

11.2
Anatomical Correlates of Neurogenic Bladder

To affect the storage and voiding functions of bladder, the connections between pons and sacral spinal cord must be intact as well as the peripheral innervation, which arises from the most caudal portion of the spinal cord. The extensive innervation is required for physiological bladder control, which includes supra-pontine inputs, intact spinal connections between pons, sacral spinal cord, and peripheral nerves.

Frontal lobe lesions usually result in involuntary bladder contraction with smooth and striated sphincter synergy. Sensation and striated sphincter functions are generally preserved. On the basis of animal experiments it has been suggested that disconnection of frontal or cingulate region from septal or hypothalamic areas allows micturition to proceed automatically and involuntarily following brain damage. Occasionally in frontal lobe lesions, there may be areflexia of bladder especially in the early stage, which may rarely persist in the chronic stage.

Pons has a crucial role in micturition because of pontine micturition center. In positron emission tomography scan studies it was revealed that successful voiding resulted in activation of medio-posterior region of pons, whereas upon unsuccessful voiding it lead to activation of ventrolateral pontine tegmentum [8]. In the cerebral cortex there was significant activity in right inferior temporal gyrus and right anterior cingulate gyrus during voiding, which was not present during withholding phase. This area of the cortex is thought to be involved in intended and planned micturition. A significant difference was noted in right cingulate gyrus, which was activated more in posterior and superior region during voiding and was reduced during withholding of voiding. This signifies that this area is involved in alertness and is activated during facilitation of micturition and its activity reduced on inhibition of micturition [8]. Urodynamic studies in patients with brainstem neurogenic bladder show detrusor hyperreflexia, low-compliance bladder, and detrusor areflexia.

11.3
Spinal Cord

Trans-spinal pathways connect the pontine micturition center to sacral spinal cord. Intact connections are important for reciprocal activity of detrusor and sphincter, which is needed to change the behavior between storage and voiding modes. Following disconnection from the pons, synergistic activity is lost which results in simultaneous contraction of detrusor and sphincter (detrusor sphincter dyssynergia, DSD). New reflexes emerge to overcome DSD to drive bladder emptying which results in detrusor hyperreflexia (DH). Following acute spinal pathology, there may be spinal shock during which bladder is acontractile. As the spinal shock abates, reflex detrusor contractions develop in response to low-volume filling. C fibers emerge as a major efferent, forming a spinal segmental reflex, which results in automatic voiding [57]. The abnormally overactive small capacity bladder is typical of spinal cord disease and clinically manifests with urgency, frequency, and precipitancy.

Spinal cord lesion between T6 and S2, after recovery from spinal shock, generally develops involuntary bladder contractions without sensation with smooth sphincter synergy but striated sphincter dyssynergia. The lesion above T6 manifests with smooth sphincter dyssynergia and autonomic hyperreflexia. The patient with spinal cord disease below S2 usually manifests with detrusor areflexia, and later, depending on the type and extent of neurological injury, various forms of decreased compliance during filling may occur. Various types of disturbances of external sphincter dysfunction may also occur depending on resting sphincter tone.

11.4
Cauda Equina

Damage to the cauda equina is likely to involve both anterior and posterior sacral roots, which contain somatic and parasympathetic fibers. The clinical picture is characterized by saddle-shaped sensory loss (S2–S4) with loss of voluntary control of anal and urinary sphincters, as well as impotence. The parasympathetic fibers in cauda equina reach the second-order neurons, which lie close to the bladder wall. In cauda equina lesions detrusor functions therefore are decentralized rather than denervated. Sympathetic innervation of bladder neck, however, is preserved in cauda equina lesions.

Interruption of the peripheral reflex arc may be very similar to those of distal spinal cord disease. Detrusor areflexia often develops with low compliance, smooth sphincter may be relatively incompetent, and external sphincter may show residual tone not amenable to voluntary relaxation. These patients are more concerned about their profound genital sensory loss or inability to defecate, rather than bladder symptoms.

11.5
Peripheral Neuropathy

The innervation of detrusor muscles is largely by parasympathetic nerves, which originate from S2 to S4 and pass through pelvic plexus and pelvic nerve. The striated external sphincter is innervated by same spinal segments via pudendal nerve. There is controversy about the sympathetic innervation of the bladder by thoraco-lumbar outflow. The sympathetic innervation of bladder neck, however, has been demonstrated by the ability to close the bladder neck during ejaculation. All three peripheral nerve components (motor, sensory, and autonomic) may be affected due to peripheral neuropathy.

11.6
Plasticity in the Context of Neurogenic Bladder

Plasticity refers to structural, metabolic, or neurological changes in which the target organs themselves influence the environment and control their functions. The neurological changes may occur at different levels, e.g., morphological, electrical, or organizational. The chronic clinical manifestations of neurological bladder may reflect the interaction of these phenomena under the rubric of plasticity. The plasticity-induced changes may be reversible to a variable extent and therefore may account for persistence of clinical symptoms after the initial stimulus for dysfunction has been corrected or removed.

The plasticity manifests with reorganization of micturition reflex after complete trans-section of spinal cord above S2 and peripheral neural organization following damage to peripheral parasympathetic denervation of lower urinary tract. In obstructive uropathy, e.g., after stricture of urethra, the molecular events are triggered by stretch or ischemia which results in increase of contractile protein synthesis and hypertrophic tissue protein [36]. Increase in ratio of type-III and type-I collagen and their location determines the release of certain growth factors from smooth muscles resulting in increased extracellular matrix and fibrosis. These changes are associated with reduced compliance and hypertrophy of bladder. The hypertrophy of bladder may be myogenic or neurogenic. Afferent neuroplasticity is induced by autoantibodies to nerve growth factors [54]. Even after removal or relief of obstruction; the bladder dysfunction may not revert and is attributed to structural changes as well as C-afferent-mediated neuroplasticity, which has been demonstrated by ice-water cystometry.

11.7
Neurogenic Bladder and CNS Infections

The common infections which may lead to neurogenic bladder are given in Table 1.

11.8
Encephalitis

11.8.1
Herpes Virus

Herpes virus (HSV) infection results in diverse neurological manifestations depending on the type of herpes

Table 1. Common infections which may lead to neurogenic bladder

Virus	Infection
Encephalitis	Herpes, Japanese, measles, mumps, enterovirus, cytomegalovirus
Myelitis	Tropical spastic paraplegia, HIV, polio
Bacterial	Meningitis: pyogenic; tubercular
	Myeloradiculopathy: tubercular; Pott's paraplegia
Parasitic	Schistosomiasis, cysticercosis
Spirochete	Lyme, syphilis
Parainfectious	Acute disseminated encephalomyelitis, transverse myelitis, Guillain-Barre syndrome

virus. HSV I produces meningoencephalitis with unique affinity for frontotemporal cortex. HSV II produces myelitis, radiculomyelitis, and brainstem encephalitis.

11.8.2
Herpes Zoster

Herpes zoster produces dorsal radiculomyelitis with generally restricted involvement. It commonly produces radiculopathy and rarely myelopathy and encephalitis (vasculitis).

11.8.3
Herpes Simplex Encephalitis

Herpes simplex encephalitis (HSE) is the commonest sporadic focal encephalitis. It is the most important viral encephalitis because of availability of specific antiviral therapy. Early diagnosis and treatment reduce mortality and morbidity. The clinical manifestations of HSE are due to frontal (behavioral abnormality, tonic clonic seizures) and temporal (aphasia, partial complex seizure, and hemianopia) cortex involvement. The involvement of frontal lobes may be associated with bladder dysfunction, which manifests with involuntary bladder contraction with smooth and striated sphincter synergy. These patients also have precipitous incontinence of both urine and stool [48]. In the acute stage there may be retention of urine. With the availability of PCR, however, the spectrum of HSE has changed and patients with mild and atypical manifestations are more commonly diagnosed. In an analysis of 1224 samples of cerebrospinal fluid 7.6% were positive for HSE of which the presentation was that of meningitis in 52%, encephalitis in 26% and atypical (mild or no focal signs) in 17%; therefore, a high index of suspicion is required for diagnosis of HSE [21]. It is conceivable that because of involvement of frontal lobes, bladder control is likely to be frequently affected, but in the available literature there is no report of bladder involvement in HSE. Two of our HSE patients had bladder dysfunction. An 8-year-old boy in the first week of illness developed retention of urine necessitating prolonged catheterization. The other patient was a 23-year-old woman whose consciousness improved after 2 weeks of acyclovir therapy but had involuntary incontinence of urine and stool. She had only 30 ml post-voiding residual urine.

11.8.4
Japanese Encephalitis

Japanese encephalitis is the commonest endemic encephalitis, which occurs both in endemic and epidemic forms in South East Asia, especially in post-monsoon period. In the acute stage the clinical picture is nonspecific. The patients manifest with fever, altered sensorium, decerebration, or decortication. Focal neurological signs may be present due to involvement of anterior horn cells and later a wide variety of movement disorders including Parkinsonian features, dystonia, and miscellaneous movement disorders such as chorea, tremor, myoclonus, and athetosis appear [39, 40]. In the acute stage, most patients, depending on the depth of coma, have retention of urine with or without overflow incontinence, and require catheterization. As encephalitis abates, the bladder functions also improve. In our study of 50 patients with encephalitis, 20 had incontinence or retention of urine in the acute stage of illness, but none of them had clinically significant bladder dysfunction after recovery from altered sensorium (unpublished observation). In the studies on sequelae of Japanese encephalitis, bladder dysfunction has not been reported as an important sequel [23, 38].

11.8.5
Brainstem Encephalitis

A number of viruses can result in the involvement of brainstem such as Japanese encephalitis, herpes, cytomegalo virus, etc. The micturition disturbances in brainstem encephalitis have rarely been reported because of severe clinical picture threatening respiration, consciousness, and cardiovascular system. As the consciousness improves and catheter is removed, micturition disturbances are noted. This was illustrated in a report of brainstem encephalitis due to HSV-I. A 45-year-old man, when recovered from unconsciousness, developed nocturnal urinary frequency, incontinence, and voiding difficulty. His MRI revealed bilateral pontine segmental lesions extending from medulla to midbrain. Urodynamic study revealed residual volume of 350 ml with detrusor hypo-reflexia during voiding. The urinary symptoms paralleled clinical recovery and improved completely by the 60th day [52]. In the early stage of encephalitis there may be detrusor areflexia because of cerebral shock.

11.8.6
HS-II Infection

The HSV-II infection has become an important venereal disease and produces two discrete neurological syndromes: meningitis and radiculomyelitis. Urinary retention due to HSV-II infection with active genital lesion has been well reported and is attributed mainly to radiculomyelitis, but associated pain may also contribute to urinary retention. Otherwise healthy young men with active genital herpes may present with acute urinary retention and signs of lumbosacral radiculomyelopathy [12]. Urinary retention from primary ano-genital herpes has been associated with impaired sensations in S2–S3 dermatomes and loss of bulbocavernosus reflex [46]. In the absence of active genital lesions acute urinary retention may still be due to herpetic infection and the diagnosis requires high index of suspicion. The cerebrospinal fluid should be examined early in the course in young patient with urinary retention. Cerebrospinal fluid (CSF) reveals lymphocytic pleocytosis, which may persist up to 3 weeks after the clinical recovery [56]. The diagnosis is confirmed by CSF PCR, ELISA, or viral culture. Cystometry reveals flaccid hypotonic bladder with sensory deficit [47]. The presence of bladder sensation without evidence of volitional contraction has been attributed to HSV-II infection. The voiding pattern returns to normal in 10–14 days in most patients with urinary retention due to primary herpes genitalis [12]. Since it is a self-limiting condition, it can be managed by clean intermittent self-catheterization. Up to 88% of patients with genital herpes have at least one recurrence [16].

HSV II also results in aseptic meningitis, and these patients may also develop urinary retention [55]. The suggested mechanism of urinary retention in patients with HSV-II meningitis is reactivation of HSV II in sacral ganglia resulting in autoimmune reaction. This reaction results in meningitis as well as involvement of motor fibers that cross through or pass near the sacral autonomic ganglia. This may also account for intact bladder sensations in these patients and help to differentiate it from HSV-II radiculomyelitis, in which the bladder sensations are absent [3].

11.8.7
Herpes Zoster

Invasion of sacral dorsal root ganglia and posterior nerve root by herpes zoster virus (HZV) may result in urinary retention and detrusor areflexia days to weeks after the primary viral manifestations. The radicular distribution of rashes is usually present, but occasionally fever and malaise, with pain in perineum and thigh, with severe constipation without rashes, may also occur. Urinary incontinence due to detrusor hyperreflexia may occasionally be reported. The mechanism of urinary incontinence in HZV infection has been attributed to nerve root irritation, meningeal inflammation, myelitis, and zoster cystitis [10]. In a report on 57 patients with HZV infection, 15 had urological manifestations, only 2 had frank urinary retention, and 3 patients had incontinence. On urodynamic study all the patients had involuntary bladder contractions, and 10 had irritative voiding symptoms of dysuria and frequency [10]. Cystoscopy may reveal vesicles in the urinary bladder mucosa akin to skin lesions. The condition subsidies spontaneously in 1–2 months and is managed by intermittent catheterization and acyclovir therapy.

11.8.8
Poliomyelitis

Poliomyelitis is of historic interest in the developed world and is becoming rarer in the developing countries as well because of mass polio immunization programs. Acute poliomyelitis may result in acute retention of urine and detrusor areflexia with intact bladder sensations. The incidence of voiding disturbances in polio was reported to be 4–42% by Bors and Comarr [9].

11.8.9
Mumps

Mumps is a common childhood infection. It results in neurological involvement and nearly 50% of children with mumps have cerebrospinal fluid pleocytosis. The neurological manifestations of mumps are nerve deafness, retinitis, opic neuritis, cortical blindness, neuropathy, myelopathy, and cerebellar ataxia. The patients with associated myelopathy may have neurogenic bladder. We reported a child with mumps myelopathy who presented with paraplegia and urinary retention. His neurological symptoms preceded the parotid swelling by 3 days. His motor and urinary dysfunctions improved rapidly after methyl prednisolone therapy. An MRI scan showed T2 hyperintensity from C3 to T12 spinal cord [5].

11.8.10
Tropical Spastic Paraplegia

Tropical spastic paraplegia (TSP) is a slowly progressive paraplegia associated with early demyelination and eventual atrophy of thoracic spinal cord following human T lymphotropic virus type I (HTLV-1) infection. It commonly manifests in third to fourth decade with female preference. Tropical spastic paraplegia is endemic in Japan and the Caribbean basin, although has also been reported from other parts of the world. A positive HTLV-I antibody in serum and CSF helps in the diagnosis [11]. Micturition disturbances are reported in 60% patients with TSP [60]. Both irritiative and obstructive symptoms have been reported and include dysuria, hesitancy, urgency, and incontinence [10, 43]. Urodynamic study reveals detrusor hyperreflexia and detrusor areflexia [18]. In a study on 50 untreated HTLV-I myelopathy patients both irritative and obstructive symptoms coexisted; 38% patients had only urinary symptoms throughout their illness. In 58% of patients the cause of frequency was found to be detrusor hyperreflexia; however, decreased bladder capacity due to large amounts of residual urine was probably another cause of frequency. Detrusor sphincter dyssynergia was the main cause of voiding difficulty. In some patients hypocontractile detrusor during voiding was also a cause of voiding difficulty. With progression of disease, the incidence of detrusor hyperreflexia and detrusor sphincter dyssynergia also increases [29]. A gradually progressive contracted bladder may be found in some patients with TSP and is attributed to lymphocytic sub-mucosal infiltration of urinary bladder [45].

11.8.11
Acquired Immune Deficiency Syndrome

The incidence of neurological complications in AIDS patients is estimated to be 30–40% [53]. In 20% patients the neurological symptoms may be the presenting manifestations of AIDS [6]. AIDS affects both central and peripheral nervous system. The neurological involvement in AIDS may be due to HIV virus infection per se or due to secondary infection, immune alteration, or associated tumors. Of 67 AIDS patients, 11 reported urological symptoms, which included urinary retention, frequency, and poor urinary flow. Urodynamic studies showed detrusor hyperreflexia in 3, areflexia in 4, as well as hypocontractile detrusor and outlet obstruction in 2 patients each. Toxoplasmosis was the commonest co-infection in AIDS patients [34]. In a prospective study on patients with HIV infection, moderate subjective voiding symptoms were present in 10%, and severe symptoms in 2%, whereas 4% patients had significant micturition problems necessitating urodynamic evaluation [26]. In another study on HIV patients, the urinary symptoms were categorized into voiding (inability to void) in 4% and storage (frequency, urgency, and incontinence) in 41% [28]. Urodynamic studies in HIV patients revealed involuntary bladder contraction, detrusor sphincter dyssynergia, detrusor hyperreflexia, and detrusor areflexia. These patients may also have urinary symptoms without neurogenic bladder because of associated urethral stricture, as they are prone to have other venereal diseases. Detrusor areflexia in HIV patient may as well be due to cytomegalovirus infection of cauda equina.

11.9
Bacterial Infections

11.9.1
Pyogenic Infections

Septic meningitis is rarely associated with spinal cord dysfunction leading to acute retention of urine. In a review covering the period 1971–2001, only 33 patients with septic meningitis had acute spinal cord dysfunction and 26 of whom were children. The organisms responsible were *N. meningitis* in 11 patients, *S. pneumonia* in 8, *E. coli* in 5, *H. influenzae* in 4, *S. Agalactiae* in 2, *Klebsilla pneumonie* in 1, and *Corynebacterium Jeikeium* in 1 patient. The neurological sequelae in these patients included bowel and bladder dysfunction, walking difficulty, and spasticity [33]. We have managed an 18-year-old boy who presented with retention of urine,

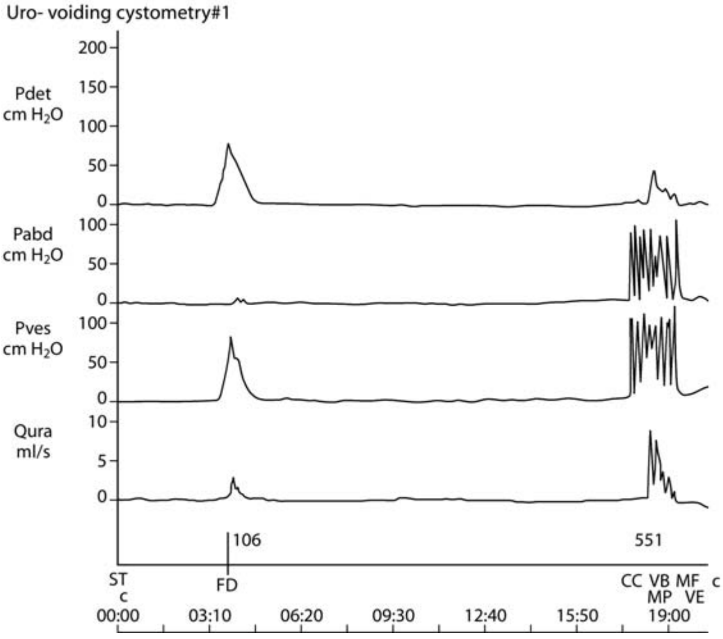

Fig. 1. Urodynamic study in a patient with neurogenic bladder as a sequel of pyogenic meningitis. Study shows detrusor contractions during filling phase, leak at 106 ml and bladder capacity was 551 ml, suggesting detrusor hyperreflexia.

ophthalmoplegia, lower cranial nerve palsy, and paraparesis due to pyogenic meningitis. His chest radiograph showed lobar pneumonia in right lower zone. He improved on IV antibiotics, but his urinary frequency and urgency persisted even after 3 years. Urodynamic study revealed detrusor hyperreflexia (Fig. 1). Epidural abscess can also present with acute spinal cord dysfunction simulating acute transverse myelitis. Brain abscess can also result in acute urinary retention. Frontal lobe abscess resulting in retention of urine followed by loss of voluntary control has been reported [62].

11.9.2
Central Nervous System Tuberculosis

Central nervous system (CNS) tuberculosis is one of the commonest causes of chronic meningoencephalitis and paraplegia in the developing world. With the appearance of AIDS, tuberculosis is being increasingly recognized in the areas where it was not an important problem. Central nervous system tuberculosis is the most dangerous form of tuberculosis and can have diverse clinical manifestations resulting in basal meningitis, meningo-encephalitis, spinal arachnoiditis, Pott's spine, and tuberculoma of brain and spinal cord. Each of these pathologies is a potential cause of neurogenic bladder depending on the extent and location of the lesion.

Mild meningitis stage I (only meningitis) and stage II (meningitis with focal signs with or without mild impairment of consciousness) are less likely to produce bladder dysfunction; however, stage III (meningitis with coma) is invariably associated with retention or incontinence of urine. There is paucity of well-designed studies in CNS tuberculosis evaluating bladder dysfunction. In a study by Eroles Vega et al., 2 patients with tuberculous meningitis with HIV co-infection, who had intra-spinal lesions and arachnoiditis, presented with subacute paraplegia, radicular pain, sensory level, and neurogenic bladder [20].

Tubercular arachnoiditis or radiculomyelopathy refers to inflammation of arachnoid alone or all three meninges, which may be acute or chronic, mild or severe, localized or extensive. The severity and extent of root or cord compression depends on the site of maximum involvement, such as cauda equina or higher lesion, which presents as single or multifocal myelopathy. The bladder symptoms depend on the anatomical distribution of arachnoiditis and include root pain, paresthesia, weakness, wasting, and bladder dysfunction. The limb weakness may be upper motor or lower motor neuron type, or mixed variety affecting lower and upper limbs in various combinations. Retention of urine may be an early or late feature.

11.9.3
Pott's Paraplegia

Pott's paraplegia is one of the commonest causes of paraplegia in the tuberculosis endemic areas. Spinal tuberculosis primarily affects the anterior part of body in paradiscal area. Damage to the vertebral body, intervertebral disc and associated paravertebral cold abscess are quite characteristic of Pott's spine. Spinal cord compression may be produced by vertebral collapse, abscess, granuloma, sequestrated bone, fibrotic band, and associated vasculitis, alone or in various combinations. Thoracic vertebrae are most commonly affected in Pott's spine. In a study on 39 patients with Pott's paraplegia, thoracic vertebrae were affected in 24, lumbosacral in 10, and cervical in 5 patients. Single vertebra was involved in 4, two in 29, and three or more in 6 patients. None of the patients had HIV co-infection and all improved on conservative treatment [41]. In a study of 32 children with spinal tuberculosis, 8 patients had paraplegia, which was associated with bowel and bladder involvement [44]. In our experience 18 of 64 patients with spinal tuberculosis had some form of micturition disturbance, which was associated with severe lower limb weakness (≤grade II) in all except one. None of the patients had HIV co-infection and all improved on conservative treatment (unpublished observation).

Intraspinal tuberculoma can result in retention of urine and later neurogenic bladder depending on the level and severity of the spinal cord involvement. In a study of 74 autopsy cases with CNS tuberculosis, only 4 had intraspinal tuberculoma [17]. With the availability of MRI, spinal tuberculosis can be detected more frequently and at an early stage. In an MRI study on spinal tuberculosis, spinal tuberculoma were found in 8 of 24 patients [25]. One of our patients with miliary tuberculosis developed acute paraplegia with retention of urine. On receiving antitubercular therapy (RHZE) and methyl prednisolone 500 mg intravenously for 5 days; his paraparesis and urinary dysfunction improved (Fig. 2) [30]. Occasionally spinal adhesive arachnoiditis may result in syringomyelia and neurogenic bladder. In a study of 9 patients with syringomyelia secondary to adhesive arachnoiditis, 4 patients had neurogenic bladder and some of them responded to shunt surgery [32].

11.10
Parasitic Infestations

11.10.1
Schistosomiasis

Of all the helminthiasis, schistosoma produces highest mortality and morbidity. It is prevalent in South America, the Caribbean Sea, Africa, Middle East, and South

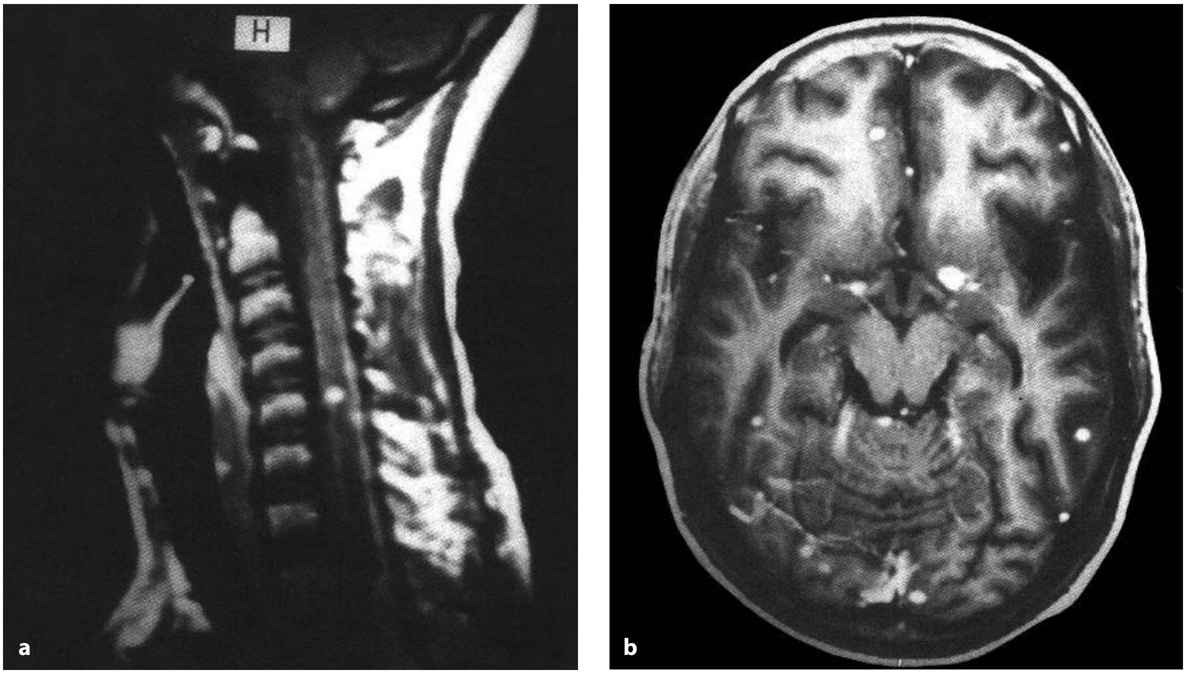

Fig. 2. **a** Gadolinium-enhanced spinal MRI of a young boy reveals a disc-enhancing lesion at C5 vertebral level as well as meningeal enhancementl. **b** Gadolinium-enhanced cranial MRI of the same patient in axial slice reveals multiple miliary-enhancing lesion and mild meningeal enhancement. He suffered from military tuberculosis and presented with acute paraparesis and retention of urine. (From [30])

East Asia. Human schistosomiasis is caused by five species: *S. mansoni*; *S. japonicum*; *S. mekongi*; *S. intercalatum*; and *S. hematobium*. Human infection is caused by penetration of skin by cercarie, which are released from infected snails in freshwater bodies. In the subcutaneous tissues these form schistosomula, which migrate within 2–4 days via veins and lymphatics reaching lung and liver. Sexually mature worms are finally discharged into the venous system at specific anatomical locations. Schistosomiasis manifests with skin, lung, liver, as well as gastrointestinal and urinary symptoms. *S. japonicum* produces cerebral granuloma and may cause partial seizures. Spinal cord involvement occurs after weeks to years of *S. hematobium* and *S. mansoni* infestations. *S. hematobium* results in transverse myelitis due to migration of ova from vesical to systemic venous plexus. In *S. mansomi*, transverse myelitis is usually a chronic complication after cirrhosis of liver. Portosystemic shunt allows *S. mansomi* larvae to migrate to spinal veins. This view, however, is unlikely to account for early spinal cord involvement by *S. mansoni* infestation. Spinal cord involvement in schistosomiasis manifests with progressive paraplegia with sphincter involvement. In acute myelopathy due to schistosomiasis, initial areflexic detrusor may normalize later or persist or may develop into detrusor hyperreflexia with or without sphincter dyssynergia. In chronic progressive myelopathy bladder involvement is characterized by detrusor hyperreflexia with sphincter dyssynergia. In a study of 9 patients with myelopathy due to *S mansoni*, the symptoms included hesitancy, frequency, incontinence, retention with or without overflow incontinence, and difficulty in voiding. Six patients had thickened bladder wall with diverticulae. Urodynamic study revealed detrusor hyperreflexia with external sphincter dyssynergia in 5 patients and detrusor areflexia and detrusor hyperreflexia without sphincter dyssynergia in 2 patients each [22].

11.10.2
Neurocysticercosis

Neurocysticercosis (NCC) is a common parasitic disease prevalent in South East Asia and Latin America. It is the commonest cause of partial seizure in the endemic areas due to involvement of cerebral cortex. It can occasionally affect the spinal cord [58]. In 8 patients with intraspinal NCC, the cysts were located in the thoracic spinal cord in 6 and cervical in 2 patients. The majority of these patients improved after surgery [42]. Another patient aged 26 years had bilateral arm pain and weakness with micturition disturbances in the form of weak urinary stream and persistent residual urine. Spinal MRI revealed intramedullary NCC in cervical and conus region. Urodynamic study revealed hyposensitive, hypocontractile bladder, and unstable detrusor muscle [19].

11.11
Spirochetal Diseases

11.11.1
Lyme Disease

Lyme disease is caused by *Borrelia Burgdoferi*. In the endemic areas it produces meningitis, meningoencephalitis, and occasionally encephalomyelitis. In a study of 44 patients with Lyme encephalomyelitis, 11 had bladder symptoms but detailed urodynamic studies were not reported [2]. Lyme disease may lead to primary urological symptoms or these may appear as late sequelae. Urinary urgency, nocturia, and urge incontinence have been reported as the common symptoms in Lyme disease. Neurological voiding dysfunction may occur as a part of neuroborreliosis as well as due to direct invasion of urinary tract though former is reported to be more common [14, 15]. Direct invasion of urinary bladder by *Borrelia Burgdorferi* can lead to sterile pyuria because of cystitis. In a study of 7 patients with neuroborreliosis, the urinary symptoms included retention, frequency, urge incontinence, and enuresis, and perineal sensory loss was present in 4 patients. Urodynamic evaluation in these patients revealed detrusor hyperreflexia in 5 patients and detrusor areflexia in 2 patients. Despite treatment with appropriate antibiotics, the urinary symptoms may recur in about 50% patients. This may be due to inadequacy of 2 weeks ceftriaxone therapy in eradicating the infection, or there may be irreversible damage to the nervous system [13].

11.11.2
Neurosyphilis

Syphilitic myelopathy is now rarely reported as a cause of neurogenic bladder in the post-antibiotic era. Loss of bladder sensation and increased residual urine has been reported in tabes dorsalis because of demyelination or atrophy of posterior spinal cord and dorsal root ganglia. In a report of 8 patients with tabes dorsalis bladder sensations were decreased in all, bladder capacity increased in 6, and cystometric capacity was increased in 3 patients. The most common urodynamic funding in tabes dorsalis was detrusor areflexia. Sphincter EMG was usually normal, as motor system is spared [27]. In another study of 8 patients with neurosyphilis, dysuria and chronic retention of urine were the most common urological symptoms and were occasionally the only evidence of neurological involvement. Urodynamic study suggested the involvement of sensory pathways, particularly posterior roots [4].

11.12
Parainfectious Demyelination

There is a wide spectrum of demyelinating disease of central and peripheral nervous system, which are temporally related to infection. These diseases are not due to direct injury by the organism, as the neurological signs appear weeks after recovery and the virus cannot be isolated from the neural tissue despite the presence of inflammation and demyelination on histopathology. Post-infectious demyelinating syndromes are usually associated with virus-like illness but can also occur after immunization, bacterial infection, surgery, and pyretotherapy. The spectrum of parainfectious demyelinating syndromes is wide, and neurogenic bladder is associated with the following:

1. Acute disseminated encephalomyelitis (ADEM)
2. Acute transverse myelitis
3. Guillain-Barre syndrome

In ADEM the demyelination is multifocal affecting cerebral white matter, brainstem, cerebellum, and spinal cord. In 11 patients with ADEM the urinary symptoms included urinary retention in 9 patients, urgency, frequency, nocturia, and difficulty in voiding in 2, and urge incontinence in 1 patient. During the follow-up period 7 of 9 patients with retention of urine were able to void. Voiding symptoms were present in 5 and irritative symptoms in 4 patients, although 6 patients had nearly complete neurological recovery but urinary symptoms persisted in 3 patients [50]. Acute transverse myelitis (ATM) is nearly always associated with bladder involvement and may be one of the most disabling sequelae despite near total recovery of neurological deficit. In a study of 18 patients with ATM, 17 had urinary retention and 1 patient had urge incontinence at presentation. Spinal MRI in 14 patients revealed T2 hyperintense signal changes exceeding three spinal segments in 13 patients and 1 patient had normal MRI. Follow-up at 6 months revealed normal voiding in 2 patients only. Retention persisted in 6 patients and storage symptoms developed in 10, 5 of whom also had voiding difficulties. Urodynamic studies in acute stage revealed areflexic or hyporeflexic bladder in 10 patients. Bladder sensation of filling was absent in 5, whereas in the remaining 5 patients it was between 91 and 505 ml. Bladder compliance was reduced in 3 patients and normal in 1 patient. The bladder capacity in this group ranged between 230 and 700 ml. In 2 patients with detrusor hyperreflexia bladder sensation was absent, compliance poor, and bladder capacity 78 and 194 ml, respectively. Detrusor sphincter dyssynergia was present in 3 patients. All the patients were followed up clinically for at least 6 months. Retention persisted in 6, normal voiding in 2, and the remaining patients had frequency, urgency, urge incontinence, hesitancy, and straining in various combinations. Urodynamic studies were repeated in 5 patients. Initial detrusor areflexia was replaced by detrusor hyperreflexia in 2 and areflexic hypocontractile bladder persisted in 2 patients, one of whom had loss of bladder sensation. In 1 patient detrusor hypereflexia persisted. At 1 year 8 patients were followed up clinically and the symptoms were similar to those at 6 months, except urge incontinence improved to urgency. The urodynamic studies were carried out in 4 patients and changed in 1 patient only; detrusor sphincter dyssynergia changed to detrusor hypereflexia (Fig. 3) [31].

Three more studies have reported bladder functions in ATM. In one study, all the patients had hypocontractile areflexic bladder; however, 3 of these patients did not have any sensory or motor deficit [1]. In another study, urodynamic tests were carried out in the acute stage in 2 of 8 patients and revealed detrusor hyperreflexia in 1 patient and detrusor external sphincter dyssynergia in the other [7]. In a study on 10 patients with ATM, 5 underwent urodynamic study and the results were somewhat similar to the above-mentioned studies [51].

There is a controversy as to whether micturition disturbances are a component of Guillain-Barre syndrome. Bladder dysfunction in Guillain-Barre syndrome was thought to be rare and was regarded as a misconception. An earlier review on clinical features of Guillain-Barre syndrome reported that micturition disturbances were present in 6–40% [59], which was close to 25% noted in the original report by Guillain et al. [24]. Micturition disturbances were present in 5 of 24 (21%) in demyelinating form and 2 of 4 (50%) in axonal form of Guillain-Barre syndrome [49]. In the patients with Guillain-Barre syndrome requiring ventilatory assistance, urinary retention was reported in one-third of patients [37]. In a study on micturition disturbances in 26 Guillain-Barre syndrome patients, voiding difficulties were present in 6, nocturnal urinary frequency in 3, and urge urinary incontinence in 2 patients, highlighting the presence of both voiding and storage dysfunction [49]. Urodynamic evaluation has been carried out in Guillain-Barre syndrome in a few studies only [35,61]. Bladder areflexia and disturbed bladder sensations were common, and non-relaxing urethral sphincter with neurogenic changes is also a common abnormality [35,61]. Urodynamic studies in 4 Guillain-Barre syndrome patients revealed disturbed bladder sensations, bladder areflexia, and absence of bulbocavernosus reflex in 1 patient each. Cystometry revealed decreased bladder volume in 2 and bladder over activity in 2 patients, one of whom had urge incontinence and the other had retention [49]. Guillain-Barre syndrome affects mainly large-diameter myelinated fibers, but pathological studies have revealed moderate to severe loss of small myelinated fibers and inflammatory cell infiltration in lumbosacral spinal roots and thoraco-lumbar sympathetic chain. The above-mentioned urodynamic findings are consistent with lumbosacral

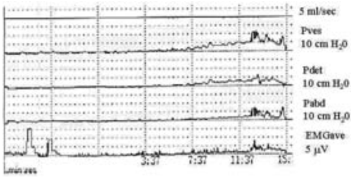

Fig.3a. Urodynamic study of a patient in acute stage of acute transverse myelitis shows detrusor areflexia with maximum vesical pressure (Pves) 20 cm of H2O and maximum detrusor pressure (Pdet) 12 cm of H2O with no voiding. EMG sphincter electromyography (from [31]).

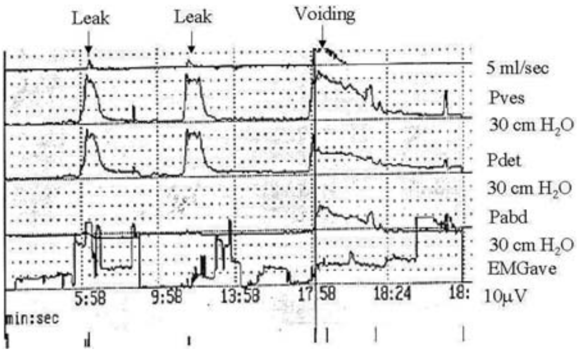

Fig.3b. Urodynamic study of the same patient at 6 months reveals detrusor sphincter dyssynergia showing repeated detrusor contraction with leakage of urine during filling phase and sphincter contraction during voiding phase. Maximum vesical pressure (*Pves*) 105 cm of H2O, maximum detrusor pressure (*Pdet*) 105 cm of H_2O. *EMG* sphincter electromyography (from [31]).

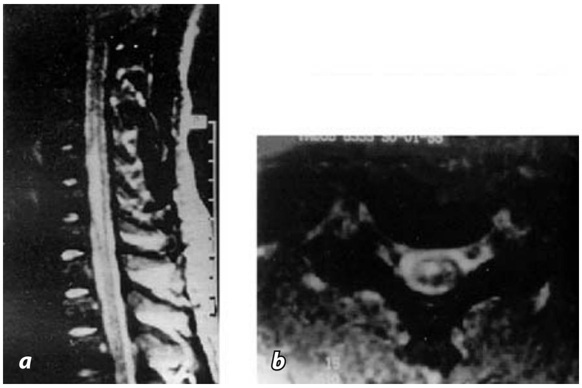

Fig.3c. Spinal T2-weighted MRI sequence shows hyperintense signal changes in cervico-dorsal region in sagittal section (*a*), which involves mostly the central part of spinal cord shown in axial section (*b*)

lesions that are found in Guillain-Barre syndrome. Occasionally, bladder over-activity and detrusor instability have been reported in Guillain-Barre syndrome. These findings are seen in suprasacral spinal cord or cerebral lesions [49,61]. These changes are regarded as being due to Guillain-Barre syndrome per se, but additional CNS lesions, ischemia, disc disease, and myelopathy should be ruled out before attributing these diseases to the peripheral nervous system.

Most of the neurological infections producing neurogenic bladder are monophasic and recover completely, or there may be persistent sequelae. Bladder symptoms improve in the majority of these patients. Control of primary CNS infection at the earliest is of the utmost important for better recovery. Management of bladder should get due attention. In the acute stage catheterization should be done depending on the post-voidal residual urine and if the patient is having coma with retention. The persistent symptoms due to neurogenic bladder following CNS infection are managed like any other neurogenic bladder and are beyond the scope of this chapter.

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Clinical Diagnosis and Evaluation

12

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12.1
Introduction

Disturbances of voiding in infants and children are often difficult to diagnose. Lower urinary tract symptoms might sometimes be generic and not always correlated to an underlying disease. In paediatric patients, congenital abnormalities and abnormal development of the neuro-vesical axis may be the cause of severe morbidity and heavy psychosocial impact [1, 2]; thus, fallout of voiding disorders on upper urinary tract, on urinary continence and ultimately on psycho-social well-being needs the attention of specialists for its early detection and management. Early recognition of neuro-vesical abnormalities enables prompt intervention and usually prevents damage to the kidneys. Spinal cord injuries and brain disorders are responsible for bladder dysfunction, but spinal dysraphism is the most common primary cause of neurogenic bladder in children and arises from a defect in the formation of the neural tube. This defect can be evident at fetal sonography and can undergo an early surgical correction at the birth. On the other hand, some children can experience a period of life apparently "free of illness", because the defect is hidden by normal skin and the spina bifida can be diagnosed only after the onset of voiding disorders; therefore, the clinical aspects and evaluation of neurogenic bladder dysfunction are related to different ages of onset.

12.2
History

All children showing any type of neurological pathology should undergo a comprehensive clinical history and physical examination. Moreover, any child with a spinal dysraphism, either hidden by normal skin or with a posterior protrusion of spinal elements, must be evaluated with a thorough assessment of urinary tracts, even if asymptomatic.

Firstly, clinical history should investigate the details of any neurological diseases or injuries, and familial medical history. Then, details of delivery and perinatal life, and the milestones of development, should be included in the evaluation. Much attention should be given to the history of age of bowel and bladder control and related habits, the latter through many questions on voiding pattern. Timing of urinary and fecal incontinence should be investigated and periods of dryness accurately recorded. Usually, the voiding history provides the greatest insight, enabling the clinician to categorize the child's incontinence in a way that allows for a tailored and pragmatic approach to management. The parents should be asked for urological history of the child. Some questions should concern the following issues:

1. The time of "potty training" (no acquiring of voiding control could suggest an incontinent bladder).
2. Strength and character of the stream (detrusor–sphincter dyssynergia, hypocontractile or areflexic detrusor).
3. The child voids spontaneously or needs a Valsalva or a Credè manoeuver to void (detrusor–sphincter dyssynergia, hypocontractile or areflexic detrusor).
4. The outflow is straightforward or seems to be an urinary leakage (detrusor–sphincter dyssynergia, poorly contracting detrusor).
5. Periods of dryness or presence of wetting between voids (retentionist or incontinent bladder, overactive bladder).
6. Urine leakage when the child laughs, coughs or sneezes (overactive bladder, bladder neck deficiency).
7. If an urgency sensations exists (overactive bladder) or if there is a lack of voiding sensation (poorly contracting detrusor, retentionist bladder or lazy bladder.

8. If there is urge incontinence (overactive bladder).
9. If the child was continent at first and afterwards had a leakage later (external sphincter deficiency).
10. If the child has had recurrent urinary tract infections (UTI; post-voiding residual or vesico-ureteral reflux).

12.3
Physical Examination

The physical examination of a child with neurogenic bladder disorders includes the abdominal, genital, perineal, anal, careful inspection of the child's back, and examination and eliciting of the sacral arc reflexes. Careful inspection of the child's back is mandatory. Haemangiomas, deep dimples, and skin tags suggest an underlying spina bifida; hair tufts suggest a diastematomyelia. Fatty masses plus pigmentation could be the physical signs of a lipomyelomeningocele. Flat buttocks with a lack of upper gluteal cleft are suggestive of sacral agenesis, often associated with atrophy of lower leg musculature.

The finding of an abdominal mass or palpable distended bladder may suggest constipation, more severe voiding condition, neurogenic dysfunction, or obstructive uropathy. The skin of genitalia may be abnormal if it is constantly wet, the bladder may promptly empty pushing the abdomen or the kidneys and bladder may be easily palpable in infants in retention. In girls, continuous pooling of urine in the vagina may be the sign of an ectopic ureter, whereas labial adhesions may result in post-voiding dribbling. In boys, meatal stenosis could be the cause of voiding and post-voiding disturbances.

Careful neurological evaluation is an essential component of the physical examination and should include an assessment of perianal and perineal sensation to pin prick and light touch, anal sphincter tone, presence or absence of a bulbocavernous and cutaneous reflex (anal wink); thus, a comprehensive neurological examination should elicit the following sacral arc reflexes: (a) the digital anal reflex; (b) the bulbocavernous reflex; (c) the suprapubic tap reflex; (d) the catheter tug reflex (only for patients with indwelling catheters); and (e) the anocutaneous reflex. Every reflex, except for the anocutaneous reflex, elicits a contraction of external anal sphincter around the examining finger inserted into the anus. Bulbocavernous reflex is elicited by squeezing the glans penis or clitoris.

Assessment of motor and sensory neurological functions of the lower extremities, along with muscle mass palpation and strength evaluation, should be carried out, especially in comparison with contralateral extremity and relative to the upper extremities. The presence or absence of deep tendon reflexes, as well as a careful inspection of the child's gait, may also provide invaluable information about underlying neurological diseases of the child.

12.4
Evaluation

The main goal of urological management in the child with neurogenic voiding dysfunction is the preservation of renal function. This is accomplished by the safe storage and evacuation of urine. Upper urinary tract function is directly impacted by lower tract function. Issues such as social continence, although often more important to the patient and family, should remain secondary to the safety of the upper urinary tracts. Starting from this point of view, the aim of the initial evaluation and diagnostic balance of patients with a neurogenic bladder is firstly to assess the uretero-vesical junction (obstructed or refluxing) and to evaluate the grade of risk of damage on renal function. Subsequently, a follow-up can be planned, managing the proper prophylactic or therapeutic regimen.

A newborn with spinal dysraphism should be assessed early for concomitant malformations, to outline the voiding pattern and to keep under control the urinary tract infections. Even if some paediatric urologists perform urodynamics at the neonatal age only in the presence of defects which can be seen by radiological imaging, most authors recommend urodynamic evaluation early in neonatal life [3–6]. Comparing radiological and urodynamic data, it is possible to apply a score for predicting the deterioration risk of upper urinary tract [7, 8]. Based on intravesical pressure (> or <40 cmH_2O), we can divide children with neurogenic bladder into high- and low-risk groups for secondary renal damage [9].

Laboratory studies, including urine analysis and urine culture, should be obtained. Though asymptomatic patients need not be treated with antibiotics, those initially presenting with pyuria and bacteruria require full evaluation. Determination of serum urea nitrogen and creatinine can be used for an initial assessment of renal function, although a more detailed baseline can be obtained by measuring creatinine clearance or, even better, performing a nuclear renal scintigraphy.

Radiological imaging of the whole urinary tract is mandatory in the evaluation of the child with neurogenic bladder. This is especially recommended before any management scheme or before surgery is planned. Baseline assessment ensures that the upper urinary tract is not damaged and that the disease is not worsened despite therapy. Frequently, in children with occult spinal dysraphism, bladder dysfunction is the only demonstrable neurological defect. Radiological study of the lumbar and sacral spine may show a subtle or clinically evident laminal defect. Magnetic nuclear resonance imaging or ultrasound in the first 6 months of life may detect a lipomyelomeningocele, a thickened filum terminalae or a tethered cord.

Ultrasound (US) scan of the kidneys and upper urinary tract provides both structural and real-time functional information. It is non-invasive, can be carried out without sedation, even in the youngest child, and does not involve radiation exposure. These features make US the ideal diagnostic procedure for frequent follow-up investigations. The first US should be performed in the first week of life to evaluate renal size and structure, cortex thickness, presence and degree of hydronephrosis and ureterectasies. Bladder volume, wall thickness and residual post-voiding volume should be measured. Repeated US at 1 month of life and then every 3 months, in the first year, allow to keep under strict control the growth of kidneys and upper urinary tract, and to eventually adjust management.

In the past, the intravenous excretory urogram was used for initial and follow-up imaging, but presently its use should be limited only to an initial evaluation, or when anatomical details could be required, such as in surgical treatment or localization of stones. Intravenous urogram could be also useful in some urological malformation, hardly detected by ultrasound, such as duplex system, horseshoe kidneys, crossed renal ectopia. The wash-out test with furosemide is recommended for the differential diagnosis between the obstructed megaureter and the ureterectasy by elevated pressure, such as occurs in the retentionist bladder with very high filling pressure.

The micturating cystourethrogram (MCUG) is also mandatory to evaluate the neurogenic bladder, even if sometimes it is impossible to obtain an image of voiding, because the child with dysraphism could be unable to spontaneously voiding. It is a more invasive test, but it is well tolerated by newborns and infants. The MCUG provides valuable clues about bladder wall thickness, bladder diverticulum, vesico-ureteral reflux (present in 30% of newborns with myelodysplasia and any abnormalities of bladder neck [10]. In some children nuclear cysto-scintigraphy might be more useful than MCUG, because it has a higher sensitivity in detecting vesico-ureteral reflux. With the advent of video-urodynamics, we recommend, when available, that MCUG be performed at the same time of urodynamic evaluation. The use of real-time video-urodynamics offers not only the static images of routine MCUG, but also the opportunity to radiologically visualize the lower urinary tract while simultaneously obtaining urodynamic data and thus obtaining a clear and precise picture of what occurs when the patient stores and empties urine. Dynamic data obtained with MCUG often allow the urologist to identify subtle problems that may be missed on routine cystometry and pressure flow study.

Radionuclide scanning provides functional data including split renal function, excretory impairments and obstructions. MAG-3 and DTPA are the most useful nuclides for a comprehensive detection and should be administrated at the first evaluation, but DMSA may be used in subsequent evaluations. A temporary urethral catheter should be passed at the time of radionuclide scanning for the best assessment of uretero-vesical junction. A child with spinal dysraphism should be appropriately investigated with ultrasound, MCUG and MAG3 scan at 1 month, and then followed with ultrasound if the patient remains well.

12.5
Urodynamics

Urodynamic evaluation provides the most accurate method of studying and classifying the neurogenic bladder; however, it is a moderately invasive procedure and therefore should be carried out only when necessary. The aim of a urodynamic test is to reproduce what the child experiences during filling and emptying of the bladder, and to record simultaneously the data about the lower urinary tract while these events are occurring. Urodynamic studies are indicated when a comprehensive evaluation of the voiding dysfunction may be in doubt, to assess the need for specific management such as surgical therapy or anticholinergic drugs, or to follow-up these interventions.

Storage impairment includes anomalies in detrusor activity, inadequate outlet closure mechanism, or both. Impairment of detrusor function can include the loss of compliance as a consequence of an increased tone or loss of elasticity of muscular fibers or bladder wall fibrosis. Another cause of detrusor impairment can be the overactivity showing as uninhibited contractions, which can alter the storage ability of the bladder. If the cause of overactivity is clearly due to neurological diseases, it is termed “detrusor hyperreflexia”. Impairment of storage and loss of bladder compliance represent the major cause of severe damage to the upper urinary tract. The higher the detrusor pressure is, the more severe will be the damage to kidneys and ureters. Detrusor pressure >40 cmH_2O is associated with a higher risk of hydronephrosis, vesico-ureteral reflux and renal deterioration [11–14].

On the other hand, incontinence could be the result of high detrusor pressure overcoming the normal urethral outlet resistance. Incontinence can also occur when the bladder neck and the external sphincter are unable to maintain an adequate outlet resistance; thus, urine leakage occurs even if the detrusor pressure of filling is normally low. Incontinence can also be the result of the inability of the external sphincter to respond to the increase in abdominal pressure.

Urodynamics can also investigate the failure to store the urine. Impairment of detrusor contractions can result in incomplete emptying or retention, which can be seen with hypocontractile or areflexic bladder. Some lesions that involve the spinal cord above the sacral micturition centre, but below the pontine micturition centre, can result in detrusor–sphincter dyssynergy [15]. The reflex relaxation of the external sphincter, which normally precedes the detrusor contraction, does not occur, and the external sphincter contracts simultaneously to detrusor; therefore, bladder emptying is obstructed. In the detrusor–sphincter dyssynergy, detrusor pressure can become dangerously high, since the contracting bladder attempts to overcome the pressure of an actively contracted sphincter. Persistence of this functional obstruction eventually results in detrusor hypertrophy, loss of compliance and, finally, myogenic failure with high storage pressures.

Bladder capacity is an important determinant of continence, by reflecting the period of time between voids. Normal bladder capacity can be estimated by either the formula bladder capacity [(age + 2) +30=ml] in older children, or [(7.0 × weight in kilograms) - 1.2 ml] in infants [16, 17].

12.6
Conclusion

Initial evaluation of children with neurogenic bladder should be as comprehensive as possible, starting from demonstration of neurogenic dysfunction to the classification of the different patterns of neurogenic bladder. Children with this condition can be categorized into high- and low-risk groups for secondary damage based on intravesical pressure. Those children with elevated pressure are at risk for hydronephrosis or reflux and evidence suggests that early management of high pressure protects the bladder from additional damage, reducing the need for eventual augmentation.

In conclusion, the following courses of action are stressed:

1. Evaluation of the upper urinary tract both morphologically and functionally for maintaining as long as possible the integrity of the kidneys. Deterioration of renal function can be prevented using some effective tools such as ultrasound, micturition cystourethrogram, intravenous urogram in selected patients and radionuclide scanning [18].
2. Evaluation of the main risk factors of deterioration of the upper urinary tract due to the impairment of bladder ability to fill and empty, which is a peculiar feature of neurogenic bladder. In these children searching for vesico-ureteral reflux is mandatory, performing MCUG or cysto-scintigraphy.
3. Evaluation of whether the management of neurogenic bladder has a positive effect on control of risk factors (intravesical high pressure during the bladder filling and post-voidal residual volume) and urinary tract infections.
4. Urodynamic evaluation of the chance of improving urinary incontinence, monitoring the effects of therapy on decreasing intravesical pressure and increasing urethral resistance [19].
5. Accurate evaluation of indications for surgery, assessing its positive role in reducing the risk of UTI, the risk due to the endovesical high pressure, and in improving urinary incontinence.
6. Evaluation of short- and long-term follow-up, the results of surgical management.
7. Critical selection of which children can achieve the best results when undergoing neurological surgery of spinal cord.
8. Evaluation of the psychosocial impact of urinary incontinence and the need for long-term therapy.
9. Attending patients in a way which enables these children to develop a sense of autonomy and better self-esteem.

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The Voiding Diary

13

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13.1
Introduction

In children with non-neurogenic bladder/sphincter dysfunction (NNBSD), free voiding studies are often sufficient in the evaluation of the condition before treatment. In children with neurogenic bladder dysfunction (NBD), on the other hand, free voiding studies, including a voiding diary and continence test, cannot be used without invasive urodynamic investigations. In fact, invasive urodynamic studies are the most important, due to the nature of NBD, with its risk of negative influence on renal function, most often due to high intravesical pressure during the filling/voiding cycle; however, free voiding studies definitely have a place in the treatment and follow-up of NBD, mainly for assessments of urinary continence both before and during treatment with anticholinergic drugs. They are also important as an instrument before surgical procedures with the aim of achieving urinary continence. In the small group of children with NBD and a normal ability to empty the bladder, free voiding studies are more important in the follow-up, which then includes checking emptying ability and voiding habits.

13.2
Normal Micturition

A healthy child is already continent from an anatomical and functional point of view from infancy, meaning that voiding takes place in distinct urine portions without leakage in between; however, social continence is not achieved until the child acquires bladder control, meaning that voiding is a conscious event, guided by voluntary impulses. Presently, there are even indications that micturition during early infancy is not only an automatic event without the influence of higher centres in the brain. It has in fact been shown that most infants wake up before voiding, indicating the existence of a connection to higher centres in the central nervous system already from birth.

13.2.1
Voiding Pattern During Infancy and Achievement of Bladder Control

Voiding by infants is characterised by a physiological form of detrusor-sphincter dyscoordination, which has been shown in free voiding studies as interrupted voidings and an increase in post-void residual [1]. This phenomenon has also been observed in urodynamic studies as an intermittent increase in the EMG activity of the pelvic floor during voiding, concomitant with fluctuations in voiding detrusor pressure [2]. A longitudinal study of the free voiding pattern from birth to the age of 3 years in healthy children revealed that the suggested dyscoordination disappears successively and is not seen after potty-training age [3]. Another important observation in the study by Jansson et al. is the increase in post-void residual during the first couple of years of life [3]. However, with the acquisition of continence, the residual volume decreased; in this group of healthy children, the ability to empty the bladder was complete at the age of 3 years.

When it comes to the achievement of bladder control, training has been regarded as unnecessary in recent decades, due to the belief that physical maturation should dictate when a child becomes dry. Moreover, the improvement in the quality of disposable napkins has contributed to a more liberal view about the age at which potty training should be started. It is quite clear from other areas, however, that training can accelerate maturation. The age at which children become dry during the day and night has increased during the past 50 years and was reported in a recent study to be a median of 3.5 and 4 years, respectively [4].

13.2.2
Bladder Capacity

In free voiding studies, no linear increase takes place in functional bladder capacity (BC) during the first 3 years of life, according to recent studies. There are two periods during which the increase is accelerated. The first step is seen during the first months of life (from 12–52 ml), whereas the second takes place during the third year of life, when the child acquires bladder control (from 68 to 123 ml) [3, 5]. The capacity is almost unchanged from a couple of months to the age of 1 and 2 years (67 and 68 ml, respectively). The second increase in bladder capacity has been considered to be a prerequisite for the achievement of both day- and night-time continence. The reason for this increase in bladder capacity has previously only been discussed in terms of general maturation.

When evaluating a child's bladder volume, it is important to consider whether it is measured during free voiding or during cystometry. In the neonatal period, cystometric capacity is lower compared with free voiding, whereas the opposite is seen after the infant year [2, 3]. This can be partly attributed to the fact that older children postpone voiding at cystometry due to the fear of voiding with a catheter in the bladder and of the unfamiliar situation of the assessment. This fear cannot be expected in the neonatal child and voiding is therefore not postponed for this reason.

At our institution, we use the expected bladder capacity (in millilitres) according to Hjälmås as a simple rule for calculation [6], since this linear increase in capacity is very similar to the non-linear increase described by Jansson et al. [3]. Furthermore, we denote a measured bladder volume of less than 65% as small for age and a volume over 150% as large for age.

It is observed that voided volume as an indicator of free voiding BC after bladder control is obtained varies a great deal, since the child decides when to void, and this can occur at any volume. Maximum BC is best measured using morning volumes or cystometric BC.

13.2.3
Number of Voidings and Urine Production

The number of voidings, urine production and bladder capacity are closely related. Urine production decreases with age in terms of millilitres per kilogram per hour (6 to 2 from preterm age to the age of bladder control). At birth, the number of voidings are one per hour, corresponding to 22–24 during a period of 24 h. As soon as the child is not fed during the night, the total number of voidings decreases to 12–15 per 24 h, even if the number during the daytime is still one an hour, as intake is also directly correlated to the number of voidings in this age group. After the age of 1 year, until bladder control is acquired, the number of voidings is still high during the daytime. The normal frequency of voiding after bladder control is achieved is considered to be five to seven voidings per 24 h [7]. The decrease in the number of voidings at the age of potty training is mainly due to the pronounced increase in bladder capacity when control of voiding is achieved [8].

13.2.4
Residual Urine

Infants do not empty the bladder at every voiding, but it is characteristic for one voiding during a period of 4 h to be complete, according to the results of 4-h observations [1]. The residual urine during a period of 4 h is more or less constant from the neonatal period until just before the age of 2 years (median 4–5 ml). During the third year, when bladder control is achieved, on the other hand, the emptying of the bladder becomes complete, so that the median residual urine is 0 ml in this age group.

13.3
Neurogenic Bladder Dysfunction

13.3.1
Voiding History

The starting point for any patient with a known neurological disorder such as myelomeningocele is the voiding history (Table 1). For those without a recognised condition in whom NBD is only suspected, the history is paramount and should be detailed thoroughly for all periods, including the prenatal and perinatal ones. The voiding history needs to be tailored to the age of the child and the questions should naturally emanate from knowledge of the normal voiding pattern for the age in question. Voiding patterns characteristic of neurological causes should raise a red flag. Examples of these pathological signs include incontinence as well as Valsalva or Crede manoeuvre at voiding [9].

Table.1. Voiding history: questionnaire

Bladder regimen	Bowel regimen
How is the bladder emptied? Spontaneously, with straining Clean intermittent catheterisation, catheter size	How is the bowel emptied? Spontaneously Type of enema, other equipment
When is it emptied? Times per day, at what time	When is it emptied? How often, at what time
In what position is it emptied? Standing, sitting, lying	In what position is it emptied? On the toilet, lying position
Bladder sensitivity? When the bladder is full In between emptyings How urgency is handled	Is there a sensation in ampulla recti? How urgency is handled
Daytime incontinence? When, type of pads, number of pads per day	Fecal incontinence? Type of pads
Nighttime incontinence Type of pad	Fecal consistency?
Urinary tract infections the last year? Urine odour, fever of unknown origin	Difficulties during emptying? Prolapse, bleeding, pain
Antibiotic treatment? Prophylactic antibiotics, no. of treatment periods the last year	Independence in bowel regimen? Need for assistance, in what way
Drugs to facilitate bladder storage? Type, dosage, treatment duration, side effects	
Other medication? Type, dosage	
Independence in bladder regimen? Need for assistance, in what way	

In children with known NBD, the first aim is to preserve kidney function. It is therefore essential to determine whether there have been any urinary tract infections (UTI). Since UTI are closely related to residual urine or infrequent emptying, the voiding pattern has to be analysed. If the child voids spontaneously, does it have bladder sensibility or void by straining? If the child's bladder is emptied by CIC, is it performed by the child or by the caregiver, which has been shown to influence the risk of infections and complications? [10] Furthermore, CIC in the lying position, as well as using catheters that are too small, may also increase the risk of UTI [10].

As the child grows, continence and independence at CIC are of great interest. Questions about urgency and the presence of wet episodes during the day and night, as well as the use of pads, are mandatory. Information must be obtained about medication with known or possible effects on the lower urinary tract. Furthermore, when drugs are used to facilitate bladder storage, the voiding history is an essential tool for follow-up. It is also important to point out that a spontaneous change in micturition and/or bowel habits could be a sign of tethered cord.

Bowel and bladder dysfunction often parallel one another in these conditions. Constipation increases the likelihood of urinary incontinence, bladder overactivity, dyscoordinated voiding, a large capacity, a bladder that empties poorly and recurrent urinary tract infection [11]. The presence of fecal incontinence, tenesmus, chronic constipation or obstipation should be recorded.

13.3.2
Registration of Voiding and Bowel Habits in Different Age Groups

13.3.2.1
Four-hour Micturition Observation

When there is a suspicion of NBD in infants and small children who are not treated with clean intermittent catheterisation, a 4-h voiding observation (Table 2) is used to investigate emptying ability and to describe the

Table 2. Four-hour micturition observation in a 2-year-old girl with tethered cord syndrome and a history of urinary tract infection. The investigation is abnormal with an increase in the number of voidings and with incomplete emptying of the bladder

Time	Voided volume (ml)	Residual urine (ml)	Food and fluid intake (ml)	Sleep	Other observations (crying, stool)
8:00					
8:10					
8:20			80 lemonade		
8:30					
8:40	28	40	Apple		
8:50	25	19			
9:00	Drops		Biscuits		
9:10					
9:20			100 lemonade		
9:30					
9:40					
9:50					
10:00					
10:10	23	41			
10:20	12	55	Banana		
10:30	15	37	10 water		
10:40	6	44			
10:50	12	47	100 lemonade		
11:00					
11:10					
11:20					
11:30	73	20			
11:40			Biscuits		
11:50	9	60	20 lemonade		Stool
12:00	58	13			

For the expected normal voiding pattern for children between birth and the age of 3 years (see Jansson et al. [3])

voiding pattern [1]. During the test, the child uses a napkin and the voiding is indicated by a gossip strip or a light signal. By weighing the napkin after each voiding, the volume is measured and post-void residual urine is checked by ultrasonography. The investigation has to include a 4-h period and not just isolated voidings, as post-void residual urine also varies in healthy babies with only occasional complete emptying [3]. In addition to residual urine, the voiding frequency and functional bladder capacity (highest sum of voided volume and residual) are evaluated.

13.3.2.2
Frequency-Volume Chart

The subjective grading of incontinence may not reliably indicate the degree of abnormality. For the objective grading of the quality of incontinence and the distribution of wetting episodes, the frequency-volume chart is used. The diary records fluid intake and urine output over several 24-h periods. It should list the number of voidings, the times of voiding, each voided volume, the distribution of voidings between daytime and night-time and episodes of leakage. It is valuable in following the results of treatment and is frequently used in the treatment of benign functional voiding disorders.

A chart which is very commonly used is the one described by Mattsson (Table 3) [7], who showed that healthy school-children could easily complete a frequency-volume chart with a high level of compliance; however, Bower et al. [12] concluded that the use of the frequency-volume chart in paediatric clinical practice does not necessarily indicate the full extent of bladder disturbance. In their study, there were some particular limitations in the compliance of patients and parents. Efforts had to be made to minimise confounding behaviours and possible sources of error. They found that the chart was unsuitable as a single screening tool. In addition to the introduction and careful explanation before it is completed, screening should include the identification of complete bladder emptying.

In the treatment of children with NBD at our unit, the frequency-volume chart is only used for those children who are urine continent. It is performed at home for 2 days. Maximum bladder capacity is often represented by the child's morning volume, whereas func-

Table 3. Frequency-volume chart in a 5-year-old girl with myelomeningocele who is able to walk and who voids spontaneously. The registration shows frequent voidings with a fairly small volume in the majority of the voidings [8]; otherwise, it is normal to have no leakage between voidings. The uroflowmetry has normally shaped curves without post-void residual. Cystometry in this girl is normal for her age.

Time	Spontaneous voiding (ml)	CIC (ml)	Dry	Wet	Fluid intake (ml)	Stool	Physical activity
06							
07	80		Yes			120	
08							Walking to school
09	85		Yes				
10						60	
11						100	Playing outside
12	95		Yes				
13						35	
14	155		Yes			20	
15	115		Yes				Walking home
16							Playing at home
17	85		Yes				
18	100		Yes				
19	60		Yes			150	
20							
21							
22							
23							
24							
01							
02							
03							
04							
05							

tional capacity can be described as the largest voided volume during the day.

13.3.2.3
Uroflowmetry and Post-Void Residual Urine

Assessments of the flow curve and measurements of the urinary flow rate have a limited value in patients with NBD, as they are only able to perform a formal micturition in exceptional cases; however, post-void residual urine is essential and should be repeated frequently in all children with NBD, both in the few who void spontaneously and in those who are on CIC. To avoid urinary tract infection, it is mandatory to ensure that the catheterisation is performed in a correct and effective manner. Some children tend to withdraw the catheter too early. There could also be a dislocation of the bladder when growing up, necessitating a change in body position during CIC in order to achieve complete emptying.

In schoolgirls treated for bacteriuria, recurrence was significantly more common in those with post-void residual urine greater than 5 ml [13]. Five millilitres in post-void residual may therefore be accepted, due to the unavoidable time delay from the end of CIC until the bladder can be examined with ultrasound. Five to 20 ml is borderline and is an indication for repeating the ultrasound.

13.3.2.4
The Pad Test

The child's suffering from being incontinent usually increases with age and differs widely from one individual to another. The pad test is a necessary complement to the voiding history and the frequency-volume chart, as it gives an objective quantitative measurement of the urinary leakage.

There are different ways to perform a pad test. The period can vary from 1, 2, 12 to 24 h. The pads can be changed and weighed every hour, and every second or every third hour when the catheterisation or voiding occurs. The test can be performed at hospital or at home and with or without diuresis provocation. In 50 children with functional incontinence, Hellström et al. compared different pad tests in which the pads were changed every hour [14]. In a 2-h ward test with fluid provocation, 70% were positive. In a simple 12-h home test, 68% were positive and, when a fluid provocation period was included in the home test, the frequency increased to 80%. Imada et al. investigated urine-incontinent children and compared 1-hour pad weighing with a test in which the pad was kept between two voidings [15]. They found no significant difference in the incidence of incontinence, but the latter method appeared to be more closely related to the clinical symptoms; however, Bower et al. have established a child-based scoring tool for quantifying urinary urgency (visual analogue scale) and one for the quantification of incontinence (Dry Pie diary) [16]. These tests have been shown to be reliable and easily administered in children with functional urinary incontinence.

In NBD the pad test has become a widely accepted tool. At our "Rehabilitation Centre for Children and Adolescents" with neurogenic bladder dysfunction, frequency-volume charts are only used for those patients who are dry. The majority of the patients are urine incontinent, at least to some extent, and, in these patients, 24-h pad tests are used. On the ward, a 1-h interval test with fluid provocation (Table 4) is performed and, at home, with parental support, a 3-h interval test with-

Table 4. A 24-h, 1-h-interval ward pad test in a 4-year-old boy who has sacral myelomeningocele. Initially, severe overactivity with leakage was seen at cystometry. After the start of treatment with oxybutynin, intravesically the leakage decreased. This pad test resulted in the dose of oxybutynin being administered at 1 p.m. instead of 3 p.m.

Time	Pad no.	Dry pad(g)	Wet pad(g)	Leakage(g)	CIC/ voiding(ml)	Urgency	Stool	Fluid intake (ml)	Activities+drugs
8:00	1	50	50	0					
9:00	2	51	51	0	140			200 breakfast	
10:00	3	49	52	3					
11:00	4	50	53	3				100	
12:00	5	49	58	9	50			150 lunch	
13:00	6	51	51	0					
14:00	7	49	80	31					
15:00	8	50	127	77	20			150	Oxybutynin
16:00	9	50	50	0			yes		
17:00	10	48	48	0				300 dinner	
18:00	11	49	58	9	88			100	
19:00	12	49	49	0					
20:00	13	50	50	0	50			300 sandwich	
	14								
	15								
	16								
	17								
7:00	Night	52	58	6	200				Sleep, oxybutynin

Formula for 24-h pad test one-hour interval:

Date

Instructions:
1. Perform CIC or void in the morning
2. Put on pad no. 1 and note the time
3. Change the pad every hour (in increasing pad number order: no. 2; no. 3; etc.) and put each one in a plastic bag and close the bag carefully
4. Void and empty the bowel as usual but note the time and the urine volume
5. Note both food and fluid intake (i.e. breakfast 200 ml milk).
6. During the afternoon, you should drink extra fluid at a volume of 13 ml/kg body weight, maximum 500 ml, on one occasion
7. Perform the activities you usually perform. Note the time and the kind of activities
8. A night pad should be put on before you go to bed
9. In the morning, the night pad should be put in the plastic bag and the bag should be closed carefully
10. All the pads will be weighed by the urotherapy unit.
11. Note type of pad: day, night
12. Note kind of voiding: CIC, times/day; straining, times/day; spontaneous, times/day
13. Note medication; type, dose and time at which intake occurs.

Table 5. A 24-h, 3-h interval home pad test in an 8-year-old boy with myelomeningocele. At cystometry, bladder capacity is 40% of that expected for age, basal pressure 20 cm of water, mild overactivity and a leakage pressure of 26 cm of water. No anticholinergic treatment is given due to side effects.

Time	Pad no.	Dry pad(g)	Wet pad(g)	Leakage(g)	CIC/ voiding(ml)	Ur- gency	Stool	Food (ml) and fluid intake	Physical activity
10:00	1	47	89	42	23			300 breakfast	
13:00	2	47	99	52	20			320 lunch	Standing up
16:00	3	47	89	42	53			250 diner	
19:00	4	47	115	68	35			200	Some aerobics
21:00	5	47	69	22	35			50 sandwich	
	6								
	7								
	Night pad	90	498	408	43				

Instructions:

1. Start in the morning with voiding/CIC, the volume does not need to be measured
2. Put on pad no. 1 and use the pads in increasing number order (nos. 1, 2, 3, etc.)
3. Change the pad each time you void or perform CIC. Put each pad in a plastic bag and close the bag carefully
4. Note the time when the pad is taken off
5. Note the time and measured voided volume
6. Note food and fluid intake, i.e. breakfast 200 ml of milk
7. Note activities during the day
8. Note medication, type, dose, and time at which intake occurs
9. The pad test is finished after 24 h and the urine volume in the morning is measured
10. Note type of pad: day; night
11. Note kind of voiding: CIC, times/day; straining, times/day; spontaneous, times/day

Table 6. Analysis of pad test

Total leakage (grams) day and day+night
Smallest and largest leakage (grams) during daytime
No. of leakages per day: dry pad; damp pad; wet pad
Total no. of pads
Longest dry period (hours)
Continence (%): dry; damp; wet
Night leakage (g)
CIC or voided volume (ml) daytime and day+night
Smallest and largest volume (ml) of CIC or voided urine
Straining (number) per day
Amount of fluid (ml) intake per day: (dry ≤2 g, damp >2 g to ≤10 g, wet >10 g)

out fluid provocation (Table 5) is performed. As noted by Hellström et al. [14], this combination produces the best results. In our opinion, a 3-h interval home test will imitate the normal day situation when it comes to incontinence more effectively than the 1-h interval ward test.

From the pad test, information (Table 6) is provided about the volume of bladder emptying and leakage, as well as when it occurs. It is important to follow urinary leakage between voidings or catheterisations during daily activity. The leakage volume and frequency are essential parameters to follow at least once a year, as changes can indicate tethering. They are also an indicator of the efficacy of treatment.

13.4
Conclusion

In children with NBD, invasive urodynamic studies are the most important due to the nature of the NBD with its risk of negative impact on renal function; however, free voiding studies, including a voiding diary and continence test, definitely have a place in the treatment and follow-up of NBD, mainly in order to assess urinary continence both before and during treatment with anticholinergic drugs and emptying ability. They are also important as an instrument before surgical procedures designed to achieve urinary continence. The starting point for any patient with a known neurological disorder, such as myelomeningocele, is the voiding history. When there is a suspicion ofNBD in infants and small children who are not treated with clean intermittent catheterisation, a 4-h voiding observation is used to investigate emptying ability and to describe the voiding pattern. Post-void residual urine is essential and should be repeated frequently in all children with a neurogenic bladder, both in the few who void spontaneously and in those who are on CIC. For the objective grading of the quality of incontinence and the distribution of wetting episodes, the frequency-volume chart is used. The pad test is a necessary complement to the voiding history and the frequency-volume chart, as it provides an objective quantitative measurement of the urinary leakage.

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Imaging Techniques in Pediatric Patients with Neurogenic Bladder Dysfunction

14

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14.1
Introduction

Prevention of renal damage and control of incontinence are the main problems in managing neuropathic bladders. The aim of imaging neurovesical dysfunction is twofold: firstly, to evaluate morphology and function of the upper urinary tract with ultrasonography, magnetic resonance urography or IV urography, or nuclear medicine; secondly, to explore bladder dysfunction and to evaluate the different causes of incontinence such as detrusor destruction, bladder atony, weakness of sphincterian resistances, vesico-sphincterian dysynergy, and uretral abnormality [1–4]. The basic radiological exam is videourodynamic combined with conventional voiding cystouretrography [2, 7].

14.2
Upper Urinary Tract Examination

Renal deterioration in neurogenic bladder dysfunction is a result of infection, reflux, and/or dilatation. It is usually avoided by emptying the bladder. Neurogenic bladder imaging needs to explore the upper urinary tract at diagnosis and during follow-up. The most useful exam is ultrasonography, which offers good evaluation of the renal parenchyma, the collecting system, and the bladder. But sensitivity is poor for the detection of vesico-ureteral reflux, even with color Doppler sonography [5].

14.2.1
Ultrasonography

The kidneys are examined in supine and prone position. The examination can be difficult because of spinal deformation and constipation in this pathology. The volume of the kidney must be recorded for the follow-up, but inter- and intraobserver variations are frequent [9]. Hydronephrosis can be observed, anteroposterior diameter of the pelvis is measured. With calyceal dilatation renal parenchyma can be reduced. Recurrent infection may lead to renal atrophy, with disappearing of normal cortico-medullary differentiation. Ureters can be dilated and may be observed in the pelvis when the bladder is full. The bladder wall may be irregular or thickened. The thickness of the vesical wall is estimated when the bladder is full. The residual urine after emptying can be evaluated with US examination [8].

14.2.2
Nuclear Medicine

Renal scintigraphy allows for global renal function and evaluation of urodynamics by IV injection of a radioactive tracer: DTPA (Tc99m Diethylen Triamin Penta Acid or Mag 3 Tc99m Mercapto acetyl triglycine). Mag 3 is the preferred tracer because of its most efficient extraction. This examination allows a semi-quantitative analysis of vascular, filtration, and excretion of each kidney.

Renal cortical scintigraphy using DMSA (dimercaptosuccinic acid) allows the detection of chronic renal cortical scarring due to urinary tract infection.

14.2.3
Magnetic Resonance Imaging and MR Urography

Magnetic resonance imaging is used to investigate the spinal cord [6]. It is recommended in children with daytime wetting when this is associated with impaired bladder sensation or failure of emptying, even if there are no neuro-orthopedic, cutaneous, or lumbo-sacral X-ray abnormalities [13].

Magnetic resonance is useful in investigating kidney because it allows evaluation of both the morphology and function. But in this type of patient, the common presence of metallic material limits the use of magnetic resonance.

14.2.3.1
T2-Weighted Sequences

Because of the long T2 of fluid in the collecting system, urine is used as the intrinsic contrast agent. With heavily T2-weighted sequences, urine within a dilated or nondilated system appears as a bright signal. Images are obtained in sagittal and coronal oblique view. To obtain sufficient distension of the collecting system, an injection of furosemide (0.5 mg/kg) is performed a few minutes before the beginning of the examination, with maximal efficacy 10 min after injection. Parenchymal scarring can also be investigated with MRI [10].

14.2.3.2
Excretory MR

Excretory MR is based on glomerular filtration of gadolinium chelate, after IV administration of a low dose, which appears as a bright signal on T1-weighted images. The nephrotoxicity is very low. Repetition of fast T1-weighted sequences, after IV administration of gadolinium, takes up to 15 min to chelate in an oblique coronal plan, providing morphological and functional information about the urinary tract. Time–intensity curves obtained from the parenchymal region of interest are similar to those obtained during renal scintigraphy.

14.3
Lower Urinary Tract Examination

14.3.1
Plain Film

Plain films are not necessary for all exams. When they are performed, they are obtained in the supine position. The aim is to visualize the lumbar–sacral spine (first examination) and to depict the presence of stones. In this case, no gonadal protection is used. A lateral film of the sacrum may be necessary if not visible on the plain film, as chronic constipation is frequent.

14.3.2
Videourodynamics Combined with Conventional Voiding Cystourethrography

14.3.2.1
Technical Considerations

Before the beginning of the exam, the bladder is emptied by spontaneous micturition, Credé or valsalva maneuvers, or intermittent catheterization. Then the volume of urine in the bladder is noted, after catheterization for residual urine.

Cystography is performed after catheterization of the urethra or after cystostomy, if a “tubeless cystostomy” or a continent conduit (Mitrofanoff technique) has been done. This procedure must be performed using a sterile technique. It is important to document whether the patient has a latex allergy, in which case special gloves need to be used. Two urethral catheters are introduced into the bladder (two 6 F, or 6 and 8 F) and left inside until the end of the examination.

Bladder filling is obtained slowly (15–20 ml/min), by instilling contrast media by gravity from a container suspended 1 m above the tabletop. The contrast media must be heated to avoid bladder stimulation. Stimulation tests, such as coughing, increasing the intra-abdominal pressure by coughing, or positional changes can be used to reproduce usual conditions and test the storage capacity of the bladder.

As few as possible films are obtained. Fluoroscopic capture can be used to avoid excessive irradiation. Anteroposterior view of the bladder is taken at the beginning of the instillation and when the bladder is full. The bladder capacity must be noted. Then films are taken in an oblique or lateral position in boys to visualize the bladder neck and the urethra when spontaneous micturition is possible.

14.3.2.2
Morphological Results

The bladder morphology is rarely normal. A verticalization of the bladder is frequently observed, due to the deformation of the detrusor. The trigone can be elevated because of a thickening of the bladder wall. The bladder neck can be spontaneously opened and the posterior urethra then becomes opacified. Abnormalities of the bladder wall, such as diverticula or trabeculation, are often clearly demonstrated. Vesicoureteral reflux can occur at any time, even during emptying (Fig. 1).

During voiding, urethrogram is obtained in oblique position in boys, and in anteroposterior supine position in girls. It can demonstrate irregularities of the bladder base and abnormally prominent bladder neck. When an usually large urethral caliber with incompletely relaxed external shincter is observed, it indicates a bladder sphincter dyssynergia.

Post-voiding imaging is not a good way to estimate a residual contrast material in the bladder, because of a non-physiological voiding (position, pain after catheterization). Then, because of physiological voiding, residual urine is better evaluated with US examination.

14.3.2.3
Urodynamic Results

The classification of neurogenic bladder dysfunction depends on different factors, including bladder pressure, compliance, activity, and contractility [11]. The cystometrogram does not test for innervation, but for the effects of denervation. The results must be interpreted after taking into account the condition of the bladder at the time of the examination (e.g., urinary tract infection). This examination requires that the child be still.

A pressure volume curve is recorded. In normal conditions, the intravesical pressure increase is progressive and regular (from 0 to 20 mm Hg) with filling. Then it increases faster with sensation of filling. During micturition pressure is high (40–60 mm Hg) and decreases quickly.

The maximal intravesical pressure (in mm Hg) is noted when the bladder is full and the quotient of volume/pressure is used to define the bladder compliance, normally between 15 and 20 in children. It is a direct reflection of the tone of the muscle: Compliance is high when the bladder is large and hypotonic (Fig. 2), and it is low when the bladder is small and hypertonic (Fig. 3). A hypotonic bladder has excessive capacity, whereas a hypertonic bladder has a diminished capacity.

Hyperactivity is defined as abnormal uninhibited contractions, appearing as spikes during the filling phase (Fig. 4). It is due to contraction of the detrusor. Sensation of filling can be present or not. When sensation is present, the patient is aware of the urge to void.

The level of pressure for micturition depends of the detrusor contractility and ureteral resistance. A normal level is 50 or 60 mm Hg. All these results must be clearly mentioned in the radiological report.

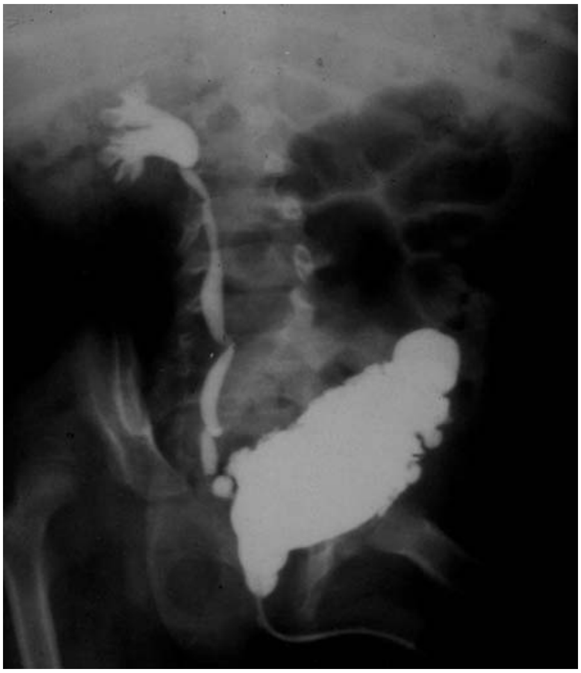


Fig. 1. Spina bifida in oblique position. Visualisation of the bladder neck which is spontaneously opened, verticalization of the bladder, abnormalities of the bladder wall with diverticula and trabeculation, right vesico-ureteral reflux

14.4
Conclusion

Imaging techniques allow us to diagnose and follow-up neurogenic bladder dysfunction [12]. Upper urinary tract is explored by ultrasound and scintigraphy or MRI. Cystography combined with cystometry allow a functional system of classifying neuropathic bladder, based on the presence or not of sensation of voiding, capacity, and compliance, and the presence or not of uninhibited vesical contraction. All these explorations are useful in deciding the type of treatment, in achieving continence, and above all, in protecting the upper tract from deterioration [3].

Fig. 2. Spina bifida. **a** Cystography shows verticalization of the large bladder, capacity 350 ml. **b** Cystometry: hyperactivity spikes (slow waves) during the examination, without leak of urine

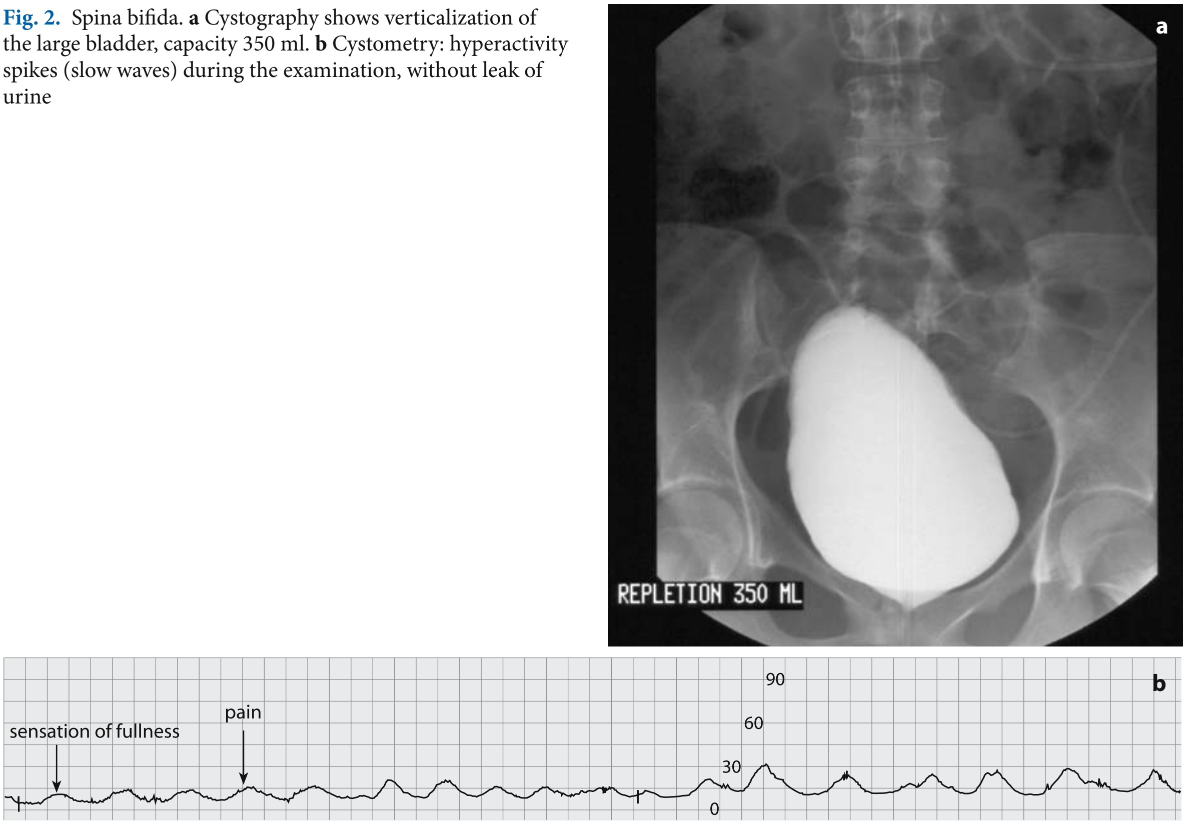


Fig. 3. Intramedullary tumor, paraplegia. **a** Cystography shows a small bladder, leak of urine after instillation of 10 ml of contrast media, capacity 30 ml. **b** Cystometry: high pressure with low compliance and hyperactivity spikes

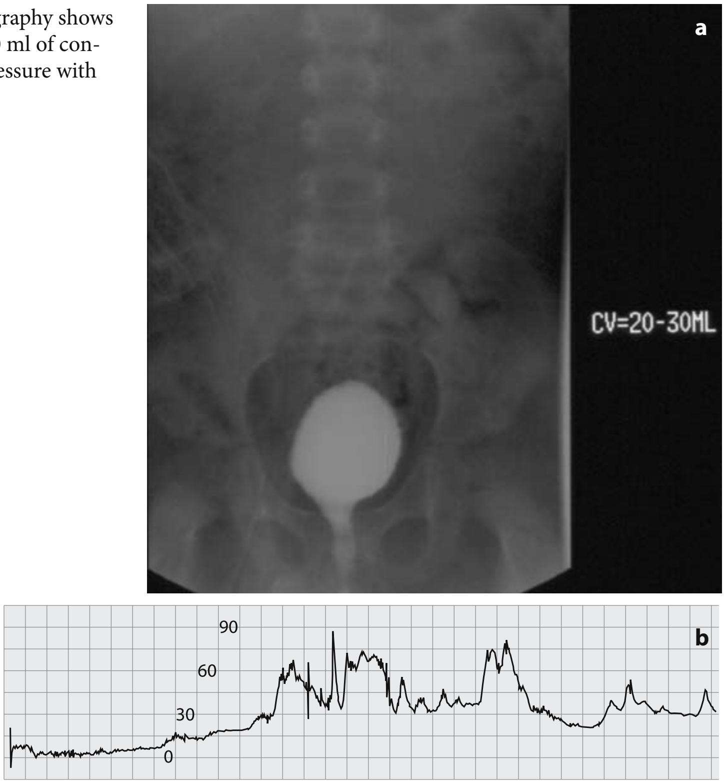
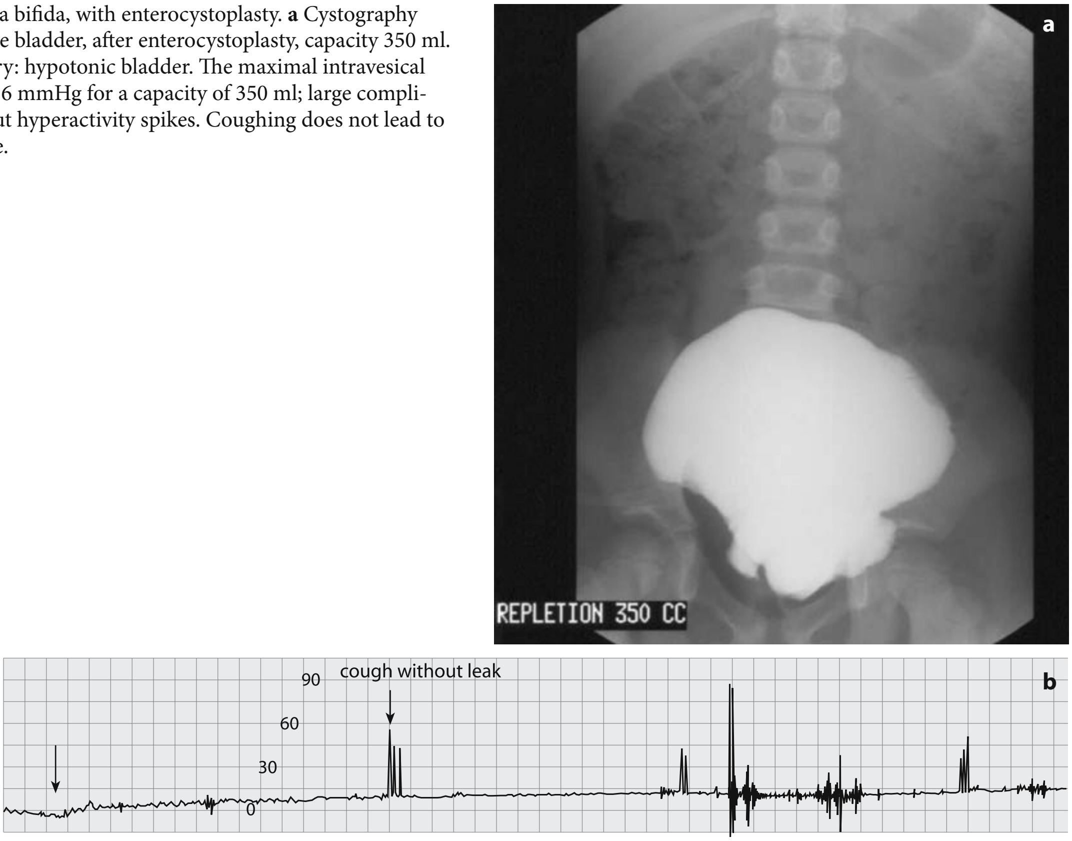


Fig. 4. Spina bifida, with enterocystoplasty. **a** Cystography shows a large bladder, after enterocystoplasty, capacity 350 ml. **b** Cystometry: hypotonic bladder. The maximal intravesical pressure is 16 mmHg for a capacity of 350 ml; large compliance, without hyperactivity spikes. Coughing does not lead to leak of urine.



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The Role of Scintigraphy in the Management of Children with Neurogenic Bladder Dysfunction

15

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15.1
Introduction

Neurogenic bladder sphincter dysfunction (NBSD) is an uncommon disorder frequently induced by lower spinal cord congenital abnormalities such as myelomeningocele (MMC). An antenatal diagnosis of NBSD can be suspected at ultrasonography (US) when hydronephrosis and bladder wall abnormalities coexist with herniation of the nervous tissue. In early childhood, apart from the lower limb paresis, the clinical expression of spinal cord anomalies can be defined by the Arnold-Chiari malformation and/or syringomyelia, being often characterized as NBSD [2]. Patients are frequently referred to the specialist for symptoms related to the incontinence and/or to urinary tract infections. In fact, congenital anomalies of the spinal cord more commonly result in a dysfunction of the lower urinary tract, affecting the control mechanism between bladder and urethra, initially sparing the upper urinary system. In these cases the progressive worsening of the upper tract's function results from a secondary damage induced by the bladder dysfunction. As consequence, urinary incontinence was judged in the past the most relevant clinical problem in NBSD and diagnosis and treatment were predominantly focused on the detrusor muscle activity [19]. Conversely, other series of MMC patients showed a higher incidence of upper tract anomalies mainly in the older children [31]. In particular, evaluating 404 MMC patients, Wilcock [35] showed an age-related increase of dilatation deformities, other than a high prevalence of primary abnormalities and true anatomical infra-vesical obstructions; thus, these findings strongly justify the great attention on urological anomalies in patients with spinal cord disorders. In particular, unexpected urodynamic changes and the consequent progressive renal failure may transform these children, also in presence of minor motor dysfunctions, in chronic patients; therefore, the close monitoring of both the bladder status and the renal function is strictly required to choose the most appropriate treatment.

On the basis of the previous observations, a complete urological evaluation, including the assessment of morphology and function of the upper and the lower urinary tract, as well as the infection status, represents the first step in a multilevel work-up, in which the nuclear medicine procedures may play an important diagnostic and prognostic role. The most important concept in the imaging of kidneys is the recognition of the intimate relationship between structure and function. Although functional and morphological procedures are generally discussed separately, none of the imaging techniques may be properly evaluated without considering the renal pathophysiology. Moreover, physiological changes in the renal function during the children's growth should be taken in account, inducing the clinician to differentiate between static and dynamic determinants.

The parenchymal function and the renal structure are usually evaluated using both hemato-chemical data, such as serum creatinine, and imaging techniques. Standard ultrasonography and nuclear imaging are at present the first-choice investigations in the assessment of the urinary system status. While a clinical role is yet demanded to traditional radiological studies, such as urography and cysto-urethrography, mainly when anatomical information is required, first results obtained by multislice computed tomography (CT), permitting a significant improvement in morphostructural and functional information, strongly suggest its recruitment in the diagnostic scenario [29]. Very important perspectives, already supported by rigorous articles but not yet evidence based by a wide experience, are connected also with the magnetic resonance imaging (MRI), while no sufficient data have been acquired to justify a reliable clinical role for US using contrast media; therefore, waiting for their larger diffusion and a further validation, new diagnostic imaging techniques using CT, MRI, and US can play a role mainly as second-step procedures. Conversely, in these patients standard US is certainly the first diagnostic approach, having completely replaced intravenous pyelography as baseline examination. In the presence of the capability to acquire a satisfactory morphostructural information major advantages, particularly relevant in pediatrics, include mainly the absence of risks connected with contrast media and ionizing radiations; therefore, a safe and effective serial evaluation can be worldwide easily achievable, and diagnosis and monitoring of pathological conditions, such as hydroureteronephrosis, renal scars, and nephrolithiasis, can be reliably achieved. In this scenario, the diffusion of nuclear medicine procedures in the diagnosis and follow-up of urological problems in infants and children has been significantly increased over the past two decades. Many aspects have contributed to this rapid growth, including the introduction of new radiopharmaceuticals and the improvement of imaging devices (gamma cameras) as well as an ever more reliable and reproducible standardization of quantitative functional parameters calculated by computer analysis. Nuclear medicine procedures are non-invasive, requiring neither fasting nor bowel preparation. They can be performed without anesthesia or sedation also in outpatients. Radiopharmaceuticals have no systemic pharmacological effects and do not cause allergic reactions. The radiation-absorbed doses do not reach a harmful range and are much lower compared with those linked with the corresponding radiological techniques. At present, the major advantage of radionuclide studies is consequent to their capability to offer either qualitative and quantitative functional information currently unavailable with other standard imaging modalities. Because many disorders of the urinary tract in children with MMC are part of a dynamic process that requires serial examinations, non-invasive radionuclide studies are a useful tool to dynamically assess the course of these subjects.

Few papers have been published to define specifically the usefulness of nuclear medicine in NBSD; therefore, to analyze the possible role of radionuclide procedures in these patients, we discuss in this chapter, with a critical analysis mainly based on our personal experience, four main issues of clinical interest in these diseases: (a) urinary tract dilatation; (b) monitoring of the renal function; (c) urinary tract infections; and (d) renal transplant. In nuclear medicine practice, static or dynamic renal scintigraphy and the direct or, less frequently, indirect radionuclide cystography, may be used to reach these different aims.

15.2
Nuclear Medicine Techniques

15.2.1
Direct Radionuclide Cystography

Direct radionuclide cystography (DRC) requires the bladder catheterization with instillation of 18–37 MBq of 99mtechnetium-pertechnetate mixed in a fixed volume (250–500 ml) of saline or irrigating solution. Dynamic images are acquired to continuously monitor the bladder activity during the filling and voiding phases. The clinical role of DRC is partially reduced by a poor anatomic detail other than by the inability to image urethral anomalies. Conversely, the standard X-ray voiding cysto-urethrography, better evaluating anatomic features and urethra, because of the need of a continuous extended observation under fluoroscopy, determines a higher absorbed dose, unjustified during the follow-up. The more favorable dosimetry together with a significantly higher sensitivity of DRC in detecting VUR strongly support its use also before cystography as a first-step procedure when an anatomical information is not requested [22].

Similarly to the other nuclear medicine procedures, neither preparation or sedation are needed. The antimicrobial prophylaxis is mandatory to reduce the risk for catheter-induced infections. The child is usually instructed to void immediately prior to catheterization. The residual volume may be measured by catheterization or by computer analysis of the bladder activity.

Sterile urethral catheterization should be performed with the largest-size Foley or feeding catheter able to pass the meatus. In our experience a 2.6-mm-diameter 8-F catheter in the large majority of patients, and a 1.8-mm-diameter 6-F catheter in infants, have been used. The Foley catheter has been only rarely chosen. In particular, in children with a neurogenic bladder, also in clean intermittent catheterization (CIC) program, our preference has been devoted to the 5- to 8-F feeding tube allowing a physiological bladder filling, mirroring the real bladder status. Conversely, the Foley's catheter may induce changes into the storage capacity and, as a consequence, the relationship between the functional bladder capacity and the beginning of the urine dribbling in non-voiding patients may not be reliably assessed.

The bladder volume for the individual patient can be approximated in milliliters according to the formula: (age in years + 2) × 30 cc. The end of the filling is achieved when the appropriate volume is reached. The filling phase may be stopped by a spontaneous voiding or for a back pressure effect (stop of the flow from the infusion bottle) in non-voiding patients [11].

In our experience a higher sensitivity in detecting vesico-ureteral reflux (VUR) has been observed using the cyclic multiple-filling technique, which has been therefore frequently preferred. This technique is performed by using a feeding tube remaining positioned during the second filling cycle. The maintenance of the catheter in place avoids additional catheterizations also allowing a recycling, when the initial fill does not permit to reach an appropriate bladder volume to assess reflux. The visual evaluation of DRC may be integrated by the quantitative measurement of refluxing and bladder volumes, other than by the calculation of the post-void residual volume. The VUR at DRC is classified into three grades: mild reflux when the tracer is seen only in the ureter; moderate, in presence of the radioactivity in non-dilated ureters and collecting systems; severe reflux is equated with a high activity in a dilated ureter and collecting system.

15.2.2
Indirect Radionuclide Cystography

Indirect radionuclide cystography (IRC) allows identification of a VUR without urethral catheterization. This technique is based on the ideal condition of a rapid and complete renal clearance of an intravenously injected agent for a dynamic renal scan, giving simultaneous information on the renal function and the bladder status. The IRC is performed at the end of a conventional dynamic study, when the activity at the level of the upper urinary tract is drained and most of the tracer is in the bladder. Serial continuous images are obtained before, during, and after voiding. A sudden increase in radioactivity at the level of the kidney or of an ureter indicates a VUR. The cinematic display with contrast enhancement and time/activity curve analysis may assist in the detection of reflux. The study is non easily performed in children with a neurogenic bladder and in those who are non-toilet drained. Because of the low sensitivity in detecting reflux this test should not be used as an initial screening test. Mild grades of reflux are difficult to be detected and a negative study has to be confirmed by direct cystoscintigraphy; therefore, IRC should be reserved to few instances, finding a rationale application when catheterization is impossible or in children with known reflux when renal scanning is part of the follow-up evaluation. The indirect method feasibility is also depending on a normal renal function and an adequate drainage, strictly requiring cooperation by the patient, who must be able to void on request.

15.3
Static Renal Scintigraphy

15.3.1
Agents

Technetium-99m dimercaptosuccinic acid (DMSA) is the best cortical imaging agent available at present, allowing an excellent visualization of the renal cortex undisturbed by a significant interference deriving from the pelvi-caliceal activity. In fact, after intravenous injection, the agent is tightly bound to the cortical tubular cells with only a small amount excreted throw the urine. As alternative to DMSA, technetium-99m glucoheptonate (GH) has also been proposed. It is cleared by a combination of tubular secretion and glomerular filtration. Because of its partial excretion in the urine, a moderate visualization of the excretory system can be evident, creating difficulties in interpreting images, mainly in presence of an obstruction in the collecting system. Nevertheless, approximately 12% of the administered dose of GH remains in the renal cortex, firmly bound to the tubular cells, providing a satisfactory visualization of the renal cortex at 2–4 h after injection. The GH is not a reliable agent for measuring glomerular filtration rate (GFR).

15.3.2
Procedures

Planar images should be acquired 2–3 h after the DMSA injection or at 4 h when GH is administered. The scan is performed with the child lying in the supine position, minimizing renal depth differences. Sandbags and Velcro straps may be utilized to reduce movement. Single photon emission tomography (SPET) increases the spatial resolution determining consequently a higher sensitivity either in the detection of small cortical defects and in the evaluation of the renal damage. Nevertheless, because of the possible increase of false-positive results and of technical problems mainly due to movement artifacts not easily recognizable, SPET is not worldwide accepted as the first choice approach with respect to the planar acquisition. A DMSA scan is considered abnormal when the split function in one kidney is 10% lower with respect to the contralateral and/or when a focal uptake defect is detected [27]. The study is recommended when small cortical lesions, such as in acute and/or chronic pyelonephritis, are suspected in evaluating the left-to-right differential uptake in congenitally small kidneys. Renal static scintigraphy can also be used in the diagnosis and/or prognostic evaluation of renal infarcts or masses, horseshoe kidney, multicystic dysplastic kidney, and ectopic kidney. The DMSA scan provides a detailed image of the renal cortex other than an accurate measurement of the split renal function. Although static scintigraphy should not be used for the measurement of absolute functional parameters (i.e., GFR), changes in the split function may assess the progression of the renal damage.

15.4
Dynamic Renal Scintigraphy

15.4.1
Agents

Iodine-hippuran-131 (^{131}I-hippuran), ^{123}iodine-hippuran (^{123}I-hippuran), ^{99m}technetium-mercaptoacetyltriglycine (MAG3), and ^{99m}technetium-diethylenetriamine-pentaacetic acid (DTPA) are the most diffuse agents available for renal dynamic imaging. These radiopharmaceuticals may be distinguished between glomerular agents (DTPA) and tubular excreted compounds (MAG3, ^{131}I-hippuran and ^{123}I-hippuran).

DTPA is the agent most widely used for dynamic renal studies, mainly because of its lower cost with respect to alternative radiocompounds. Its initial transit through the kidney reflects renal perfusion with the uptake measured between 1 and 3 min after injection proportional to the renal function. Renal clearance of DTPA is determined by glomerular filtration in absence of significant tubular secretion or of cortical retention; therefore, its clearance rate can provide an accurate measurement of the glomerular filtration rate (GFR). The rapid DTPA clearance and the consequent high concentration in the urinary tract also allow the evaluation of pelvi-calyceal system, ureters, and bladder. Because of its low extraction rate and retention in the renal cortex, this agent fails to detect small cortical lesions.

I-hippuran-131 is mainly a tubular agent. Almost 80% of the intravenously injected radiocompound is extracted from the blood and secreted by the renal tubular cells. The remaining 20% is excreted by passive glomerular filtration. Despite these excellent biological properties, ^{131}I-hippuran has a major limitation, particularly critical in pediatrics, due to the beta emission, determining a high radiation exposure and unsuitable images. Significantly higher quality images and a lower radiation dose, in the presence of an identical favorable pathophysiological behavior, can be obtained using as label the pure gamma emitter ^{123}iodine. Moreover, ^{123}I-hippuran is the agent of choice for estimating effective renal plasma flow (ERPF). Nevertheless, the high cost and the short half-life of ^{123}iodine, creating difficulties in a standard routine utilization, strongly contain its use in clinical practice.

At present, MAG3 is the most effective agent for dynamic renal imaging, being characterized by the capability to produce better high-quality parenchyma and excretory images compared with DTPA, at a lower cost and with a more favorable availability with respect to ^{123}I-hippuran, determining a lower radiation dose in comparison with ^{131}I-hippuran. This tubular agent apparently clears at a lower rate than hippuran not being filtered by the glomerulus. Although MAG3 allows an ERPF measurement with a lower accuracy than hippuran, it can be used for a reliable quantitative evaluation of the renal function.

15.4.2
Procedures

The standard procedure for dynamic renal scintigraphy requires a correct hydration 15 min before the scan. The MMC patients, especially if enrolled in CIC programs, should be catheterized to empty the bladder and to ensure an adequate drainage, avoiding false-positive obstructive renograms. After the intravenous injection, a 20-min dynamic study is acquired. The renal perfusion (1–60 s), the parenchymal (1–3 min), and the excretory phase (4–20 min) are assessed and differentiated for a clinical evaluation.

Regions of interest (ROI) are drawn over the abdominal aorta, the kidneys, and a background area to plot time-activity curves. The obtained renograms give a direct representation of the different renal phases, producing different pattern in vascular, parenchyma, or excretory anomalies. The split renal function and other functional parameters, such as GFR or ERPF, are calculated in the interval 1–3 min after tracer injection. Moreover, in patients with hydronephrosis, a furosemide test may be combined to the renal dynamic scan in order to differentiate obstructed from non-obstructed kidneys.

15.5
Indications

15.5.1
Urinary Tract Dilatation

The functional infravesical obstruction due to the detrusor-sphincter dyssynergy represents one of the main problems in patients with an over-activity of the urethral sphincter. Patients with a coexistence of sphincter over-activity and detrusor inactivity may show overflow at high opening pressures other than high values in the functional capacity. Conversely, the presence of an over-activity of both sphincter and detrusor muscle produces a wider range of urodynamic patterns. In many of these cases the bladder sphincter function still remains compensated, but the increase of the bladder capacity may be an early signal of a decompensation and of a consequent obstructive uropathy [8]. In NBSD patients the urinary tract dilatation is frequently due to VUR. Moreover, functional obstruction and VUR and the urinary tract dilatation may occur in patients with spinal cord disorders also in presence of a minimal motor dysfunction; therefore, in these subjects, because of the high risk of a renal injury, a multidisciplinary approach based on voiding cystourethrography (VCUG) or DRC, a dynamic renal scintigraphy, and serial US and urodynamic evaluations appear to be strongly justified. On the other hand, when a low risk to develop a renal damage is predictable, a routine diagnostic strategy based on US, with further examinations performed only to answer to a specific clinical demand, may be considered sufficient. In a recent series, using a multiple diagnostic approach in patients with MMC evaluating 162 renal units, 57 of 127 low-risk units at the time of the diagnosis were shifted to the high-risk group for arising hydronephrosis or infections during follow-up [15]. In particular, the presence of a post-void urinary residue other than an urinary dilatation have been determined as a predictor of future renal disease. With regard to this issue, US and urodynamic are the keystones to define the diagnostic strategy. Moreover, during the childhood urodynamic procedures, because of their invasiveness, these procedures can be justified in high-risk patients at the diagnosis, but not as cost/effective techniques which are frequently repeatable in follow-up. Conversely, US is the best imaging approach for a serial evaluation, giving useful information on the bladder and the ureteral status. Furthermore, although changes in the renal size calculated at US may be utilized to follow the progression of nephropathy, functional aspects, earlier predictor of the disease evolution, including major prognostic information, may not be achieved. The plasma creatinine assay can add complementary information to define the functional monitoring, but it fails in quantifying the split function or in diagnosing a unilateral disease not affecting the overall renal function. In this scenario, to reach these goals, a major role can be certainly interpreted by dynamic renal scintigraphy (DRS). In fact, DRS is able to give reliable and reproducible information on (a) split renal function, (b) progression of the renal damage also estimating parenchymal transit time, and (c) the presence of hydronephrosis with a further distinction between dilatation and obstruction when the diuretic test is performed. A sufficiently rigorous calculation of absolute total quantitative functional parameters (GFR or ERPF) can also be obtained, mainly in presence of a non-seriously altered renal function.

The major clinical interest of DRS in evaluating disease progression, acting in a multidisciplinary strategy also involving US and hemato-chemical data, is devoted to the split-function measurement. To reach this goal also DMSA can be used reliably. With respect to the DMSA scan, DRS presents an integrative advantage deriving from its capability to assess the renal function by quantifying the tracer's renal extraction and its renal transit time. These functional parameters are very useful as accurate indexes of nephropathy, also in the initial phase, the delay in the transit time being an early signal of the increased pressure in the collecting system other than of a first loss or a disarray of nephrons. When hydronephrosis is observed, diuretic DRS can demonstrate the presence, the extent, and the severity of dilatation, also allowing the quantitative assessment of the residual renal function [13]. For these reasons this test is a worldwide-accepted method to assess patients with hydronephrotic kidneys.

The provocative diuretic test is based on the hypothesis that the prolonged tracer retention in a dilated but non-obstructed system depends on a reservoir effect. While in this case the diuretic administration should determine a prompt tracer washout, conversely in obstructive hydronephrosis the tracer still remains in the collecting system, in the absence of a significant washout. Because bladder fullness and pressure, as well as VUR during the scan, may affect the quickness of diuretic response, the use of an indwelling bladder catheter to reduce the influence of these conditions is strongly suggested [14]. Different protocols based on a different timing of furosemide administration with respect to the radiotracers have been proposed; between them, the most frequently utilized are those with the furosemide injection 20 min after the tracer (F+20), 15 min before the radiocompound administration (F-15), and simultaneously to the radiotracer at the beginning of the study (F0). There is no general consensus at present on the best protocol. It has to be pointed out, however, that F0 protocol is gaining popularity, especially in the young child because, in comparison with alternative approaches, a single injection is required giving similarly reliable results with a shorter acquisition time with respect to F+20 [5]. To reduce false-positive results and/or equivocal responses in neonates and infants, the importance of additional views after a gravity-assisted drainage is emphasized [10, 36]. Typical obstructed and non-obstructed patterns are usually diagnostic.

As previously mentioned, VUR often underlies a urinary tract dilation in NBSD; therefore, its diagnosis represents important criteria in selecting high-risk patients. Moreover, approximately 50% of the patients with upper urinary tract infections are affected by VUR, although renal infection is not the single mechanism to produce a renal failure. In NBSD patients the detrusor-sphincter dyssynergy results in a high-pressure VUR, whereas patients with pelvic pavement inactivity are characterized by a low-grade VUR with a spontaneous resolution [17, 32]. Van Gool et al. reported an incidence of 23% of VUR in patients with overactive sphincter, whereas the 14% of VUR was detected in subjects with inactive urethral sphincter. Furthermore, they observed that 95% of VUR was at high-pressure in overactive sphincter patients, also determining a high rate of renal scarring [33]; therefore, the diagnosis of VUR and the monitoring of a self-resolving low-grade VUR is mandatory. Many authors have demonstrated that DRC is significantly more accurate than VCUG and cysto-sonography in detecting VUR, even when moderate-severe VUR is taken in account [28].

We are unable to state whether the better accuracy of DRC in detecting VUR depends on the continuous monitoring of the bladder status; however, DRC may be considered the method of choice in the diagnosis of VUR also for its reliability in unmasking occult reflux, although it is ineffective in the evaluation of the male urethra.

The large variability in the percentage of detection of reflux could be explained by an intrinsic variation in the reflux itself depending on issues as therapy, different pathological conditions, and different imaging techniques utilized. Moreover, reflux is a dynamic, intermittent phenomenon, and a considerable amount of reflux may vanish within very few seconds; therefore, an examination not showing reflux may be interpreted as a test where no reflux has been demonstrated. Detection of an exclusive reflux may be promoted by the combination of different techniques or cyclic examinations, which can add the inconvenience of an increased radiation dose and cost.

In conclusion, the main indications of DRC are the initial evaluation for reflux of females with UTI, and the follow-up evaluation after a medical strategy, to assess the results of an anti-reflux surgery, to serially evaluate a bladder dysfunction.

15.6
Monitoring of Renal Function

Renal clearance of a substance can occur by two processes: glomerular filtration or tubular secretion. The glomerular filtration rate (GFR) is probably the most representative parameter of the renal function. It is relatively constant during standard conditions and, as opposed to the tubular secretion, is independent by the urine flow.

Since technetium-99m DTPA is excreted almost exclusively by glomerular filtration, its rate of clearance from blood is an accurate measure of GFR. A variety of methods may be used to calculate GFR using technetium-99m DTPA based on single compartmental analysis of the DTPA clearance. There is excellent correlation between this technique and 24-h urinary creatinine clearance [6]. Absolute GFR of each kidney can then be calculated by multiplying the total calculated GFR in milliliters per minute by the percentages obtained from the renal differential function [26]. This method of GFR calculation is relatively non-invasive and obviates the need for 24-h urine collection. Because of the need for multiple venous punctures, however, the test is unpleasant for children and their parents. Because of uncertainty about the effect of diuretics on the GFR in different pathological states, the test cannot be performed in conjunction with diuretic renography. Other methods of calculating GFR based on external counting without blood samples or with a single blood sample have been developed and are presently the most popular approach in pediatrics because of their greater acceptance by the children without losing significantly the capability to obtain reliable quantitative values [25]; however, similar reliable results in monitoring the renal function have been also demonstrated by using MAG3 scan [20].

The evaluation and follow-up of renal function are very important tools in patients with a spinal cord pathology with neurovesical dysfunction frequently followed by a renal failure; therefore, it is essential to carefully monitor renal morphology and function. In particular, we have reported in 54 patients with MMC an high rate (41%) of smaller kidneys with a creatinine clearance (CrCl) lower than 120 ml/min. In these patients the ERPF values, estimated during MAG3 scan, were significantly correlated with the CrCl ($p<0.05$) [9]. Furthermore, we have observed that a reliable quantitative estimation of the single kidney may be achieved during MAG3 scan. Indeed, GFR or ERPF determination has to be considered each time a renal impairment is suspected, even in cases when plasma creatinine values are in the normal range.

15.7
Inflammatory Disease

Neurogenic bladder lesions can change during the first 3 years of life, especially during the first year, and these changes can be missed (e.g., patients with synergy can silently develop dyssynergy) [34]. The central clinical problem in these patients with UTI is renal disease, because it is the kidney that has to bear the consequences of the infection. This should always be kept in mind when diagnosing and planning treatment for children with UTI and reflux. Urinary tract infection with or without VUR can lead to renal scarring. Children with scarred kidneys are predisposed to hypertension and chronic renal failure. The DMSA scan can be performed to evaluate either the acute phase of UTI and the chronic renal damage (6 months after the last infection). Ultrasounds can exclude anatomical problems in acute UTI, but a lower accuracy in the detection of the chronic renal damage is reported.

15.7.1
Acute Pyelonephritis

Acute pyelonephritis (APN) is a common febrile illness of children which may result in an irreversible renal damage. When bacteria enter the papilla, causing liberation of destructive enzymes and free radicals, an inflammatory response occurs in the renal parenchyma. Arterial vasoconstriction, parenchymal ischemia, and swelling ensue can be determined. The APN is usually diagnosed on the basis of clinical signs and symptoms, but the clinical presentation can be atypical and therefore diagnostic imaging can be requested. Excretory Rx-urograms are of limited value in the early detection of acute pyelonephritis showing a sensitivity lower than 30% of all the cases [4].

In this setting, US allows the identification of structural renal abnormalities, both congenital and acquired. Moreover, US is the ideal tool as initial screening investigation in children with UTI, because of non-invasive and non-utilizing ionizing radiations. Conversely, major disadvantages are the operator dependence and the lack of a functional information. Using US to diagnose APN a high sensitivity in presence of a low specificity has been demonstrated [18, 23].

Similarly, Power Doppler US is significantly less sensitive and specific than other imaging modalities (DMSA, spiral CT, MRI) as demonstrated by an experimental study in pigs [21]. False-positive or negative results are determined mainly by technical factors, such as interference from intestinal gas, breathing motion, and rib artifacts. False-negative results are also observed during the early phase of acute pyelonephritis when a partial venous obstruction due to the edema increases the blood flow through the involved part of the kidney.

Animal and human studies have established renal cortical scintigraphy as being a highly sensitive and specific method for detecting renal cortical abnormalities [3, 24]. Several papers have demonstrated that in many cases renal scars can only be detected by renal cortical scintigraphy with respect to standard alternative procedures [1, 7]; therefore, cortical scintigraphy can be recommanded as the gold standard for the diagnosis of APN, and it is proposed as a routine procedure in children with acute UTI when imaging techniques are requested. In particular, the acute DMSA scintigraphy has an important clinical role in children with a normal scan not requiring prophylaxis and/or cystography. Moreover, acute DMSA might help in defining the group with a major risk in developing renal failure [12].

15.7.2
Permanent Renal Damage (Chronic Pyelonephritis)

The DMSA scintigraphy is recommended as the technique of choice for the evaluation of renal scars, giving important diagnostic and prognostic information, defined upon detection of patients with an increased risk to subsequently develop systemic hypertension and renal impairment [30]. Reliability of DMSA findings has been confirmed by pathological studies in pig models. Six months after the acute event, the interval permits us to reliably consider DMSA abnormalities as permanent sequela [16].

A different capability to diagnose focal or diffuse renal scars at US has been reported. When used to assess a focal scar, US demonstrated a sensitivity of 5.2%, a specificity of 98.3%, a positive predictive value (PPV) of 50%, and a negative predictive value (NPV) of 75.8%; conversely, in detecting diffuse renal scarring, a sensitivity of 47.2%, a specificity of 91.8%, a PPV of 60.8%, and a NPV of 86.6% have been observed [23].

Cortical imaging with radionuclides not only permits a better diagnostic accuracy compared with US, but also allows a quantitative evaluation of the relative renal function (not possible with ultrasonography), a very important tool in grading the renal damage. The semiquantitative value of the split renal function is an important clinical marker in the follow-up to evaluate the possible progression of the disease especially in children with recurrent UTI associated with VUR and reflux nephropathy.

15.8
Renal Transplant

The NBSD in patients with neural tube defects is one of the most important causes of renal failure, requiring renal transplantation. Possible complications following renal transplants can be classified into two general categories: those due to a parenchyma failure, such as acute tubular necrosis (ATN), rejection and infection; and those due to mechanical injuries, including complete or partial obstruction of blood vessels, ureteral obstruction, urinary leak, and lymphocele. Ultrasonography, including Doppler procedures, is the first-step procedure in the detection of nephro-urological complications in transplanted kidneys. At scintigraphy, different patterns of rejection and ATN have been described. Rejection can be more frequently associated with a poor perfusion of the kidney or a reduced renal uptake also in presence of a persistent capability to continue urine formation. The differential diagnosis of rejection has been complicated by the widespread use of cyclosporine, determining a possible renal damage not easily differentiable. The distinction between rejection and ATN is difficult to assess on a single study, and serial scan over several days or weeks may be required. To exclude rejection in the serial examinations perfusion and function should improve or remain unchanged. In contrast, deterioration of the renal perfusion and function due to the rejection, if untreated, is generally progressive. Patency of the anastomosis, such as a complete renal arterial or venous occlusion, can also be assessed with a perfusion study as part of a dynamic scintigraphy focused on the quantitative analysis of the first transit of the tracer from the aorta and iliac artery to the transplanted kidney. The renal time-activity curve is compared with that of the aorta or iliac artery. A normally perfused transplanted kidney shows a sharp rise and fall in the renal time-activity curve, which closely parallels the aortic curve.

15.9
Conclusion

In conclusion, although only few papers extensively evaluated the clinical relevance of radionuclide procedures in patients with NBSD , their usefulness can be demonstrated both in diagnosis and in the prognostic definition. The most important issues deriving from nuclear medicine are related to its capability of providing reliable functional information, often quantitative, original, and/or complementary with respect to the other diagnostic approaches; therefore, in the presence of major advantages in comparison with traditional Rx, having capability to integrate morphostructural information achievable by US and waiting for a wider diffusion and a further validation of data obtained using newer procedures allowed by multislice CT and MRI, nuclear medicine can certainly find a clinical relevance in patients with NBSD.

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16

Urodynamics

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16.1
Introduction

In the presence of a child with micturition disorders, an important question should arise: “Has the child a real neurological defect or is it a normal expression of the development course?” The answer is not easy. As a result of maturation, children usually become continent during the daytime by the second year and at night by the fourth year; therefore, when assessing lower urinary tract function in children, it is important to take into account the dynamics of the maturing central and peripheral nervous system, the learned habits of bladder and bowel emptying and all the social influences affecting the child’s behaviour. The diagnostic accuracy to detect paediatric lower urinary tract dysfunction (LUTD) depends on the following factors:

1. Knowledge of the whole possible underlying neurological diseases
2. Knowledge of the overall issues concerning nervous system maturation and sphincteric control
3. Suitable neurophysiological and urodynamic equipment

As far as the aetiological classification of LUTD is concerned, the disturbances of pertinent nervous or psychological control can be classified as follows:

1. Congenital malformation of the central nervous system (CNS), including myelomeningocele, occult spinal dysraphism, caudal regression sequence (e.g. syringocele, diastematomyelia, sacral malformations, certain cases of anal atresia) and tethered cord syndrome
2. Developmental disturbances, including urge syndrome, dysfunctional voiding, mental retardation and delayed psychomotor development, and add-like syndromes
3. Acquired conditions, including cerebral spasticity (perinatal asphyxia), progressively degenerative diseases of the CNS associated with central spasticity (e.g. Hallervorden-Spatz disease), multiple sclerosis, Guillain-Barré syndrome, radiculitis, transverse myelitis, spinal cord trauma, spinal cord infections (e.g. schistosomiasis), tumours (e.g. sacrococcygeal teratoma), vascular malformations of the spinal cord and iatrogenic trauma to the pelvic plexus).

Besides the above-mentioned neurogenic causes of paediatric LUTD, there are other several non-neurogenic causes affecting children’s lower urinary function (LUT), such as:

1. Congenital disorders of smooth and striated muscle function (Duchenne’s muscular dystrophy, spinal muscular atrophy, neuronal dysplasia, i.e. megacolon–magalocystis syndrome)
2. Acquired disorders of smooth and striated muscle function (chronic bladder distension, overdistension injury, fibrosis of detrusor and bladder wall)
3. Congenital structural abnormalities (extrophy, epispadias, hypospadias; caudal regression sequence, e.g. cloaca; ureteroceles and other abnormalities of

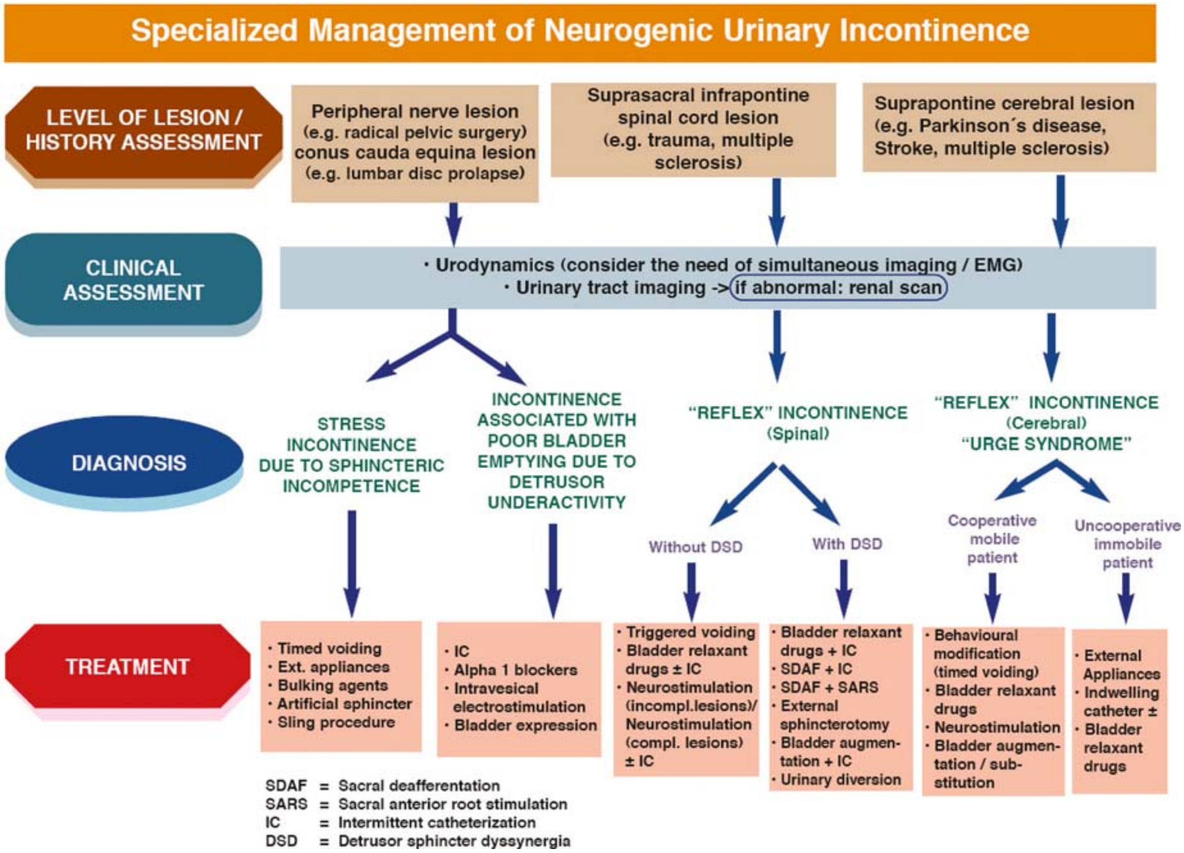

Specialized Management of Neurogenic Urinary Incontinence
LEVEL OF LESION / HISTORY ASSESSMENT
Peripheral nerve lesion (e.g. radical pelvic surgery) conus cauda equina lesion (e.g. lumbar disc prolapse)
Suprasacral infrapontine spinal cord lesion (e.g. trauma, multiple sclerosis)
Suprapontine cerebral lesion (e.g. Parkinson´s disease, Stroke, multiple sclerosis)
CLINICAL ASSESSMENT
· Urodynamics (consider the need of simultaneous imaging / EMG)
· Urinary tract imaging -> if abnormal: renal scan
DIAGNOSIS
STRESS INCONTINENCE DUE TO SPHINCTERIC INCOMPETENCE
INCONTINENCE ASSOCIATED WITH POOR BLADDER EMPTYING DUE TO DETRUSOR UNDERACTIVITY
"REFLEX" INCONTINENCE (Spinal)
"REFLEX" INCONTINENCE (Cerebral) "URGE SYNDROME"
Without DSD
With DSD
Cooperative mobile patient
Uncooperative immobile patient
TREATMENT
· Timed voiding · Ext. appliances · Bulking agents · Artificial sphincter · Sling procedure
· IC · Alpha 1 blockers · Intravesical electrostimulation · Bladder expression
· Triggered voiding · Bladder relaxant drugs ± IC · Neurostimulation (incompl.lesions)/ Neurostimulation (compl. lesions) ± IC
· Bladder relaxant drugs + IC · SDAF + IC · SDAF + SARS · External sphincterotomy · Bladder augmentation + IC · Urinary diversion
· Behavioural modification (timed voiding) · Bladder relaxant drugs · Neurostimulation · Bladder augmentation / substitution
· External Appliances · Indwelling catheter ± · Bladder relaxant drugs
SDAF = Sacral deafferentation
SARS = Sacral anterior root stimulation
IC = Intermittent catheterization
DSD = Detrusor sphincter dyssynergia

Fig. 1. Algorithm for the specialised management of neurogenic urinary incontinence. (From the Second Consultation on Incontinence, 2001)

bladder, trigone and bladder neck; posterior urethral valves and other urethral abnormalities; prune-belly syndrome; ectodermal dysplasia; disorders of collagen, e.g. Ehlers-Danlos)
4. Acquired structural abnormalities (traumatic and iatrogenic injury, hypercalciuria)
5. Unclassified conditions (giggle incontinence, Hinman syndrome, Ochoa syndrome)

A child with neuropathy complaining of urinary incontinence and/or other lower urinary tract symptoms (LUTS) should consult a specialist without attempting any initial empiric management. As part of the specialised assessment, the measurement of urine flow in children old enough and the ultrasound estimate of the post-void residual urine, together with urodynamic studies, and the upper urinary tract imaging, are highly recommended (see Fig. 1). Moreover, together with neurophysiological investigations, urodynamics may help to make a differential diagnosis between neurogenic and non-neurogenic LUTD.

16.2
Neurogenic LUTD Classification

The neurological control of the bladder is complex and needs the action of both autonomic and somatic nervous systems. Aimed at facilitating the understanding and management of LUTD, many classification systems based on neurological, urodynamic or functional considerations, or on a combination of these, have been proposed. In 1974 Bradley described four integrated complex loops regulating bladder function [3]:

1. Loop 1, characterised by inhibitory nervous pathways connecting the frontal cortex (pre-rolandic) to the pontine-mesencephalic centres
2. Loop 2, characterised by neurological pathways that link pontine micturition centres to parasympathetic sacral centres with a stimulatory effect
3. Loop 3, which coordinates the action between detrusor function and sphincter activity (pelvic nerve–pudendal nerve)
4. Loop 4, characterised by neurological pathways linking frontal cortex to pudendal nuclei

Based on that integrated neurological control system, Lapides described, in a recognisable shorthand, the clinical and cystometric conditions of many kinds of neurogenic bladder dysfunction (Table 1) [9]. According to Lapides' classification, a *sensory neurogenic bladder* is the result of a pathology that made selectively a break in the sensory fibres connecting the bladder to spinal cord and/or upper nervous centres (e.g. diabetes mellitus, tabes, pernicious anaemia). There was a loss or reduced perception of the bladder distension. When there was a decompensation of the bladder, high post-void residual urine volumes occurred with a flat cystogram profile, high compliance, large bladder capacity and low filling pressure.

A *motor paralytic bladder* is due to diseases that destroyed the motor parasympathetic nerves supplying the bladder. Possible causes were pelvic trauma, extensive pelvic surgery and herpes zoster virus infection. The range of symptoms was variable, from the inability to start and sustain a normal voiding to painful urinary retention. During the pressure/flow study the patient was unable to void voluntary. Chronic distension resulted, and when the detrusor decompensation occurred, there were a flat cystometric curve, a low bladder filling pressure and a large post-micturition residual volume.

An *uninhibited neurogenic bladder* is characterised, symptomatically, by frequency, urgency and incontinence. From the urodynamic point of view, there is a detrusor hyperreflexia (currently named "neurogenic detrusor overactivity"; see later) at low filling volumes, sometimes associated with detrusor–sphincter dyssynergia (DSD) due to a spinal cord lesion. Cerebrovascular accident, brain and/or spinal cord tumours and demyelinating diseases could cause this kind of bladder dysfunction. The DSD was characterised by involuntary contractions of the external urethral sphincter during an involuntary detrusor contraction. It was caused by neurological lesions between the brainstem (pontine micturition centre) and the sacral spinal cord (sacral micturition centre, including traumatic spinal cord injury, multiple sclerosis, myelodysplasia and other forms of transverse myelitis. According to Blaivas' classification three main types of DSD are described [2]:

1. In type 1 a concomitant increase in both detrusor pressure and sphincter EMG activity may occur. At the peak of the detrusor contraction the sphincter suddenly relaxes and unobstructed voiding occurs.
2. In type 2 there are sporadic contractions of the external urethral sphincter throughout the detrusor contraction.
3. Type 3 is characterised by a "crescendo-decrescendo" electromyographic pattern of sphincter contraction which results in urethral obstruction throughout the entire detrusor contraction. Without proper treatment over 50% of patients with DSD develop serious urological complications within about 5 years.

Table 1. The Lapides classification of neurogenic lower urinary tract dysfunction (NLUTD)

NLUTD classification
Sensory neurogenic bladder
Reflex neurogenic bladder
Uninhibited neurogenic bladder
Autonomous neurogenic bladder
Motor paralytic bladder

According to Lapides' classification a *reflex neurogenic bladder* describes a condition of post-spinal shock after a complete interruption of the sensory and the motor pathways between spinal cord and the upper nervous centres [9]. Causes might be traumatic spinal cord injury, transverse myelitis and extensive demyelinating diseases. The patient was unable to start micturition voluntarily, bladder sensitivity was absent and there was a DSD.

An *autonomous neurogenic bladder* is characterised by a complete motor and sensory separation of the bladder from the spinal cord, due to extensive damage to the sacral nerve roots and pelvic nerves. This urinary dysfunction is present in patients with spinal shock. The characteristic cystometric pattern is initially similar to the late stages of the motor or sensory paralytic bladder with a marked shift to the right of cystometric filling profile and a large vesical capacity at low intravesical pressure; however, bladder compliance and capacity are variable in relation to inflammatory chronic events, patient ability to increase intravesical pressure and resistance of the urethral sphincters during this pressure increase.

In 1979 Krane and Siroky described a classification of detrusor and sphincter coordination observed during urodynamic evaluation in patients with NLUTD [8], focusing their attention on the functional interaction between detrusor and urethral sphincter. Few years later, Wein proposed a functional classification which listed bladder dysfunction in terms of whether the produced deficit was primarily one of the filling/storage or the voiding phase of micturition [17]. In 1989 Fall et al. proposed a more detailed classification of the overactive detrusor [4], and more recently Flisser et al. described a further (video)urodynamic classification of patients with symptoms of overactive bladder [5], having a good concordance with the previous urodynamic classification suggested by Fall [4]. Flisser et al. [5] stratified patients into four categories, according to patient degree of awareness, bladder control and sphincter function:

1. Type 1: no evidence of involuntary detrusor contractions
2. Type 2: presence of involuntary detrusor contractions and patient aware and able to abort them
3. Type 3: presence of involuntary detrusor contractions and patient aware and able to contract sphincter but not abort contractions
4. Type 4: contractions present and patient unware and unable to contract the sphincter or abort contractions.

In 2002 the International Continence Society ICS (ICS) separated the storage and voiding phase describing the urethra and detrusor functions in each phase by specific designations (see later) [1].

Madersbacher et al. presented a very simple classification based on the clinical concept that the important differentiation in the diagnosis exists between the situations of high and low detrusor pressure during the filling phase and urethral sphincter relaxation and non-relaxation or DSD in the voiding phase (see Fig. 2) [11].

The number of classification systems proposed means that, to date, a perfect classification system for NLUTD is not yet available. Neurogenic classification systems, by nature, cannot describe the LUTD completely, and vice versa. Individual variations exist in the NLUTD caused by a specific neurological lesion; thus, for any particular patient the description of the NLUTD should be individualised. Because Madersbacher et al.' [11] classification system is the easiest one for general use in clinical diagnosis of NLUTD, it is currently recommended for clinical practice.

16.3
Urodynamics: Standardisation of Terminology and Technique

The bladder and the urethral complex represent the anatomic and functional unit of the micturition cycle. Their interaction allows to obtain opposite and alternating functions, such as the storage and the voiding urine phase. As far as the nervous control is concerned, the lower urinary tract is functionally controlled at several levels of the CNS. In children the coordination and communication between these levels are not fully developed until the age of 4 years. The main aim of paediatric urodynamics is to reproduce the physiological micturition model of each investigated child as thoroughly as possible, without any sedation, in a welcoming, calm, non-embarrassing environment. Tubes, needles, sore and/or bothersome stimuli may be the cause of the child's mental distress, anxiety, fear and lack of cooperation, which could invalidate the urodynamic evaluation; hence, the child's collaboration is very important to obtain reliable results, the interpretation of which would be otherwise very hard. On the other hand, paediatric urodynamics should be performed by dedicated skilled operators, able to distinguish between artefacts and physiological responses, and always ready to repeat or modify the study according to the emerging findings; therefore, the age-dependent neural maturation and the impact of the environment factors make the definitions of LUT function in children far less standard than in adults.

Aimed at standardising and better defining LUTD in children, in 1998 Nørgaard et al., on behalf of the In-

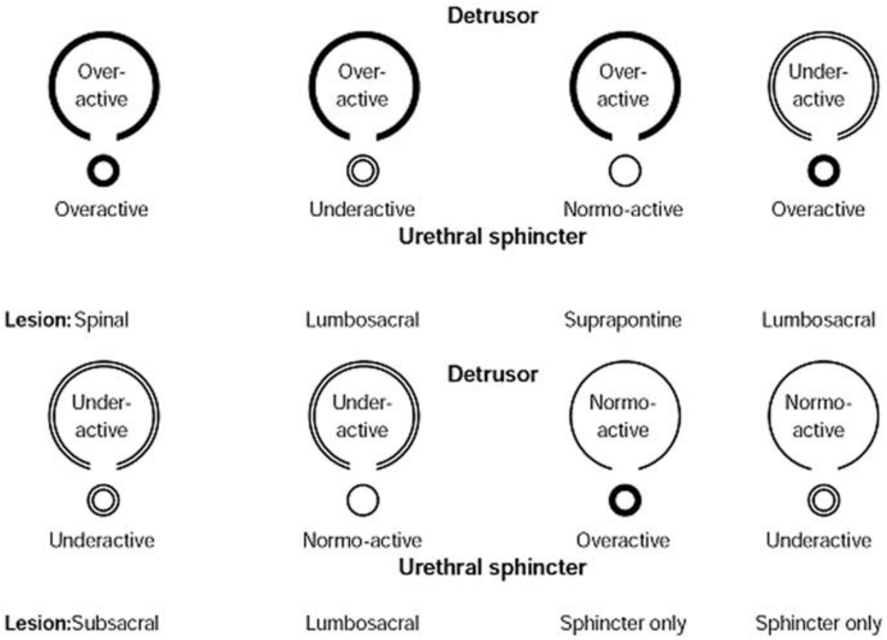


Fig. 2. Madersbacher's classification system with typical neurogenic lesions

ternational Children's Continence Society (ICCS), published a separate report about this topic [14].

More recently, the standardisation sub-committee of the ICS redefined the standardisation of terminology of LUT function [1], presenting definitions of symptoms, signs, urodynamic observations and conditions associated with LUTD and urodynamic studies (UDS), for use in all patient groups from children to the elderly.

According to the latter standardisation of terminology, urodynamic findings are defined as observations made during urodynamic studies, without representing any definitive diagnosis of a disease or condition, because they may occur with a variety of symptoms and signs, or even in the absence of any symptoms or signs [1].

There are two main methods of performing an urodynamic investigation:

1. Conventional UDS usually carried out in the urodynamic laboratory and involving an artificial filling
2. Ambulatory UDS defined as a functional test of the lower urinary tract, utilising natural filling, and reproducing the subject's every day activities.

When used in small children, conventional UDS may show some drawbacks. The unfamiliar environment of the urodynamic laboratory and the presence of the urodynamicist may trigger distress in young patients, hampering their cooperation during the study. Moreover, the "unphysiological" rate of artificial filling inevitably changes the natural behaviour of a small infant bladder, causing significant restraints on the interpretations [7].

On the contrary, ambulatory UDS, using portable data-storage devices, provides a more physiological technique for continuous monitoring of bladder function, under nearly natural conditions. There is the disadvantage that data can be analysed only retrospectively after transferring the recorded signals to a computer. Children's behaviour is unpredictable and often the young patients are not able to report all specific events occurring during ambulatory urodynamics, making the retrospective analysis of pressure recording difficult and sometimes impossible. To overcome this inconvenience, Yeung proposed a continuous real-time ambulatory urodynamic monitoring using infrared telemetry [20]. Using this technology, during urodynamic investigation, the infant may conduct normal activities, completely mobile and undisturbed, accompanied by the mother in a private room. At the same time, in the next room, the urodynamicist may observe all of the patient's activity, through a one-way mirror, while continuous real-time on-line pressure signal displays are recorded and monitored using a computer and marking particular events as necessary.

16.3.1
Filling Cystometry

Filling cystometry is the method by which the pressure/volume relationship of the bladder is measured during bladder filling [1]. Pressure flow studies of voiding are the methods by which relationship between pressure in the bladder and urine flow rate is measured during bladder emptying. During filling cystometry (as well as during the pressure flow studies) the following measurements must be detected:

1. Intravesical pressure (pressure within the bladder)
2. Abdominal pressure (pressure surrounding the bladder, estimated from rectal, vaginal, extraperitoneal or bowel stoma pressure)
3. Detrusor pressure (the component of intravesical pressure created by passive and active forces in the bladder wall; it is estimated by subtracting abdominal pressure from intravesical pressure)

Before cystometry all systems are zeroed at atmospheric pressure, and residual urine should be aspirated. Any post-void residual volume should always be confirmed by repetitive investigations. In congenital spinal cord lesion patients, bladder emptying rarely alters the child's behaviour. In that situation it is possible to drain and measure the post-void residual without any particular difficulty. Bladder access may be suprapubic or transurethral. Patient position can be supine or sitting, but in some children it is useful to put the patient in standing up position. Catheters should be small enough (≤6 Ch), and all their characteristics and catheterisation modalities should be always specified. During the urethral catheter insertion it is possible to evaluate the urethral sensation, and to measure and record the post-void residual. In children with incomplete spinal cord lesions and intact urethral sensitivity, the suprapubic access is advisable. During cystometry the child should ideally be at ease, familiarising himself with the urodynamic laboratory, the physician and the technician(s), before the investigation takes place [14]. Any distress during the investigation should be noted. The child should be awake, avoiding any drugs potentially affecting the bladder function. Any variation should be specified. As a rule, at least two cycles of filling cystometry should be recorded [1]. In children the transitional form-filling phase and voiding phase are not as marked as in adults; therefore, in paediatric urodynamics, to avoid missing this important transition, cystometry and pressure-flow/electromyography measurements should be performed as one continuous study [14]. In neurogenic children, urodynamics should continue until good filling and voiding models are obtained [7].

The fluid medium should be saline 0.9% at 25–36°C, with no additive. The ICCS does not recommend CO_2 as fluid medium in children [14]. Currently the saline filling rate is no more classified as slow, medium and fast, but preferably as physiological (less than the predicted maximum filling rate calculated by dividing the predicted maximum body weight in kilograms by 4) or non-physiological (greater than the predicted maximum filling rate) filling rate.

A physiological filling rate is recommended in children, as certain cystometric variables, such as compliance, may be significantly altered by the speed bladder filling. Moreover, filling pumps should have a preset safety switch, which makes the pump inoperative at bladder pressure of >100 cmH_2O [14]. Older children should be educated to not urinate during bladder filling, which should be carried on as long as the child shows a strong desire to void, a discomfort or starts to void. To better define the bladder storage function an accurate description of bladder sensation, detrusor activity, bladder compliance and bladder capacity is recommended [1].

Bladder sensation is difficult to evaluate in children, and only in toilet-trained cooperative young patients is this a relevant variable. Currently, terms used to define bladder sensation during filling cystometry include:

1. Normal bladder sensation
2. First sensation of bladder filling (when the patient first becomes aware of the bladder filling)
3. First desire to void (the feeling that would lead the patient to pass urine at the next convenient moment, but voiding can be delayed if necessary)
4. Strong desire to void (a persistent desire to void without the fear of leakage)
5. Increased bladder sensation (an early first sensation of bladder filling, or an early desire to void, and/or an early strong desire to void, which occurs at low bladder volume and persists)
6. Reduced bladder sensation (when the individual perceives a diminished sensation throughout bladder filling)
7. Absent bladder sensation (when the individual has no bladder sensation during filling cystometry)
8. Non-specific bladder sensation (the individual is aware of bladder filling, perceiving it as abdominal fullness or vegetative symptoms)
9. Bladder pain (felt suprapubically or retropubically, usually increasing with bladder filling, and sometimes persisting after voiding)
10. Urgency (a sudden compelling desire to pass urine, difficult to defer).

In children with LUTD it is very important to know how the detrusor works. In patients with neurogenic LUTD (NLUTD) it is rare to have a normal detrusor function (i.e. a bladder filling with little or no change in pressure, and without any involuntary phasic contractions). Often an urodynamic observation of detrusor overactivity occurs. It is characterised by involuntary detrusor contractions during the filling phase. They can be spontaneous or provoked by provocative manoeuvres, which are techniques used during UDS to provoke detrusor overactivity (e.g. rapid filling, cooled medium, postural changes, hand washing). An involuntary detrusor contraction may assume a characteristic phasic wave form (phasic detrusor overactivity) or be a single involuntary detrusor contraction occurring at cystometric capacity which cannot be suppressed, often resulting in incontinence and bladder emptying (defined as "terminal detrusor overactivity"). Urinary incontinence due to an involuntary detrusor contraction is defined as detrusor overactivity incontinence.

According to the aetiology, detrusor overactivity may be further qualified as follows:

1. Neurogenic detrusor overactivity, when there is a relevant neurological condition (this term replaced the previous one of "detrusor hyperreflexia")
2. Idiopathic detrusor overactivity when there is no defined cause (replacing the previous term of "detrusor instability").

It is possible that a combination of the above-mentioned urodynamic observations lead to other urodynamic patterns, mainly in children with spinal cord diseases.

Table 2. Standardised glossary concerning bladder capacity during cystometry

Bladder capacity during cystometry	Definition
Cystometric capacity	The bladder volume at the end of filling cystometrogram, when permission to void is usually given. The cystometric capacity is the volume voided together with any residual urine
Maximum cystometric capacity	In patients with normal sensation, the volume at which the patient feels she/he can no longer delay micturition (has a strong desire to void).
Maximum anaesthetic bladder capacity	The volume to which the bladder can be filled under deep general or spinal anaesthetic and should it be qualified according to the type of anaesthesia used, the speed of filling, the length of time of filling, and the pressure at which the bladder is filled.

The relationship between change in bladder volume and change in detrusor pressure is termed "bladder compliance". It is calculated by dividing the volume change (ΔV) by the change in detrusor pressure (Δpdet), during that change in bladder volume. It is expressed in ml/cmH_2O. To calculate bladder compliance two standard points should be used: (a) the detrusor pressure at the start of bladder volume and the correspondent bladder volume (usually zero); and (b) the detrusor pressure and corresponding bladder volume at cystometric capacity or immediately before the start of any detrusor contraction causing significant leakage.

Both points are measured excluding any detrusor contraction. Table 2 shows bladder capacity definitions during filling cystometry. In children maximum cystometric capacity (MCC) is the volume in the bladder at which the infant or child starts to void. This value is derived from volume voided plus residual volume. The MCC values should be interpreted in relation to normal values for age, using the following equation [14]:

$$y=30+(30x),$$

where y is MCC expressed in milliliters and x is the age in years. Abnormal values are expressed as percentage differences (positive or negative) from normal, using the equation [14]:

$$[(MCC_{obs}-MCC_{norm}) / MCC_{norm}(x100)],$$

where MCC_{obs} is the observed value and MCC_{norm} the normal value calculated from the child's age.

During filling cystometry, a normal urethral closure mechanism allows to maintain a positive urethral closure pressure during bladder filling even in the presence of increased abdominal pressure, although it may be overcome by detrusor overactivity.

This mechanism may be competent or incompetent. In that latter situation, the urethral closure mechanism allows a leakage of urine in the absence of a detrusor contraction.

Concerning the urethral function, during filling cystometry it is possible to detect another two urodynamic observations: (a) urethral relaxation incontinence (leakage due to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity); and (b) urodynamic stress incontinence (involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction).

16.3.2
Urethral Pressure Profile

In children with neurogenic bladder dysfunction, urethral function measurements may have a role, being helpful to discover sphincter incompetence in the presence of electromyographically normal pelvic floor activity; otherwise, there are few data in the literature justifying these measurements in non-neuropathic children. Table 3 shows the parameters used to assess the urethral function during filling cystometry.

16.3.3
Pressure Flow Studies

The assessment of bladder voiding has to be described in terms of detrusor and urethral function, by measuring urine flow rate and voiding pressures. Urinary flow

Table 3. Assessment of urethral function during filling cystometry

Variables	Definition
Urethral pressure	The fluid pressure needed to just open a closed urethra
Urethral pressure profile	A graph indicating the intraluminal pressure along the length of the urethra
Urethral closure pressure profile	Obtained subtracting the intravesical pressure from urethral pressure
Maximum urethral pressure	The maximum pressure of the measured profile
Maximum urethral closure pressure	The maximum difference between the urethral pressure and the intravesical pressure
Functional profile length	The length of the urethra along which the urethral pressure exceeds intravesical pressure in girls
Pressure transmission ratio	The increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure
Abdominal leak-point pressure	The intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction
Detrusor leak-point pressure	The lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure

Table 4. The urine flow parameters

Parameter	Definition
Flow rate	The volume of fluid expelled via the urethra per unit time (in ml/s)
Voided volume	The total volume expelled via the urethra
Maximum flow rate	The maximum measured value of the flow rate after correction for artefacts
Voiding time	The total duration of micturition, including interruptions
Flow time	The time over which measurable flow actually occurs
Average flow rate	The voided volume divided by flow time
Time to maximum flow	The elapsed time from onset of flow to maximum flow

Table 5. The pressure measurements during the voiding phase of the urodynamic evaluation

Measurement	Definition
Premicturition pressure	The pressure recorded immediately before the initial isovolumetric contraction
Opening pressure	The pressure recorded at the onset of urine flow
Opening time	The elapsed time from initial rise in detrusor pressure to onset of flow
Maximum pressure	The maximum value of the measured pressure
Pressure at maximum flow	The lowest pressure recorded at the maximum measured flow rate
Closing pressure	The pressure measured at the end of the measured flow
Minimum voiding pressure	The minimum pressure during measurable flow
Flow delay	The time delay between a change in bladder pressure and the corresponding change in measured flow rate

Table 6. Detrusor activity during the voiding phase

Detrusor activity	Definition
Normal	Normal voiding achieving by a voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span, in absence of obstruction. For a given detrusor contraction, the magnitude of the recorded pressure rises depending on degree of outlet resistance
Abnormal	
Detrusor underactivity	A detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span
Non-contractile detrusor	A detrusor that cannot be demonstrated to contract during urodynamic studies
Post-void residual	The volume of urine left in the bladder at the end of micturition

pattern may be (a) continuous (without interruption), or (b) intermittent (when the flow stops and starts during a single visit to the bathroom in order to void).

The continuous flow curve is defined as a smooth arch shaped or fluctuating when there are multiple peaks during a period of continuous urine flow. Table 4 shows the urine flow parameters to be used in children who are old enough. To measure whole pressures recorded during pressure flow studies, we have to take into account the following measurement parameters, applicable to each pressure curve: intravesical, abdominal, and detrusor pressure.

Table 5 summarises the pressure measurements during the voiding phase of the urodynamic evaluation.

Table 7. Urethral function during the voiding phase

Urethral function	Definition
Normal	An urethra that opens and is continuously relaxed allowing the bladder to be emptied at a normal pressure
Abnormal	
Bladder outlet obstruction	A generic term for obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure
Dysfunctional voiding	An intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated muscle during voiding, in neurologically normal individuals
Detrusor sphincter dyssynergia	A detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle
Non-relaxing urethral sphincter obstruction	Usually occurs in individuals with neurological lesions, characterised by a non-relaxing, obstructing urethra resulting in reduced urine flow

During micturition the detrusor, as well as the urethra, may have a normal or an abnormal function. Abnormal detrusor activity during the voiding phase may be subdivided in detrusor underactivity and acontractility (see Table 6). An abnormal urethral function during bladder emptying may be due to either obstruction to urethral overactivity, or to anatomic abnormality, such as enlarged prostate or urethral strictures (see Table 7).

16.3.4
EMG Study During Pressure Flow Studies

Electromyography (EMG) of pelvic floor striated muscles may give useful information to diagnose NLUTD. The EMG is a tool to record the electrical potential generated by the depolarisation of muscle fibres. As an isolated test it can identify a neuropathy by analysing individual motor unit potentials. To do this, needle electrodes placed directly into the muscle mass are used. They record the action potentials from discrete motor units, and are indispensable for studying single unit potentials, but they are not suited for continuous monitoring during urodynamics in children. Isolated EMG should be interpreted in the light of the patient's symptoms, signs, physical findings, as well as urological and urodynamic investigations.

Continuous EMG recorded during urodynamic studies is widely used in paediatrics, and may contribute to better assessment of the synergy between detrusor and sphincter function. In the storage phase, it is helpful to test pelvic floor reflexes. In the voiding phase, it is used to monitor urethral activity during bladder emptying. This EMG registration is performed using surface electrodes applied to an epithelial surface as close to the muscle under study as possible. They detect action potentials from groups of adjacent motor units underlying the recording surface. For clinical purposes skin electrodes are widely used in children, and usually are positioned symmetrically left and right from the external anal sphincter. Surface electrodes are not suited for studying the single unit potential and thus they should not be employed to diagnose neuropathy. Anal and vaginal plug electrodes are not well tolerated by children and should be avoided [14].

16.3.5
Videoudynamics

Videourodynamics combines a routine urodynamic study with X-ray or ultrasound imaging. It is used for children with complicated LUTD due to a neurological condition. Most of the advantages of videourodynamics derive from the simultaneous measurement of pressure and visualization of the anatomy, allowing an immediate detection of other lower and urinary tract gross anatomical abnormalities [7]. An incompetent bladder neck or an inadequate urethral closure during bladder filling, or the location of urethral obstruction during voiding, can be documented directly. A leakage of contrast medium can be demonstrated fluoroscopically. A dyssynergia between detrusor and external sphincter or bladder neck can be documented. Moreover, the external urethral sphincter mechanism, and especially in not very collaborative children, is evaluated better than with EMG.

Videourodynamics show some disadvantages, such as the following:

1. Several studies often need to obtain reliable results, especially in children with neurogenic dysfunction.
2. Radiation exposure.
3. High initial and running costs.
4. Less comfortable condition for the patient.

It is possible to drastically reduce X-ray exposure examining the child only for few seconds per minute during the filling phase (to assess the bladder shape, the bladder neck competence and the presence of reflux). During the voiding phase it is important to observe the onset of micturition and the emptying phase as much as possible to appropriately evaluate the outflow [7].

Ultrasound videourodynamics eliminate the disadvantage of the exposure to radiation. Nevertheless, a direct contact of the ultrasound transducer with the patient's body is requested, and large probes, placed intrarectally, may change the anatomical condition in the studying area [7]. Other disadvantages are: (a) inability to observe the upper urinary tract synchronously; and (b) inability to visualize the whole urethra including the region of the striated urethral sphincter, especially in male patients.

It is important to remember that some urodynamic observations are normal in younger children. Involuntarily detrusor contractions are "normal" in children who are still not toilet trained. A beak-shaped bladder base is a common radiological finding in children less than 2 years old, and may be occasionally noticed in 6- to 7-year-old children with a large congenital bladder neck, in the absence of stress urinary incontinence, usually without any particular pathological significance. Finally, it should be kept in mind that most children, within an adult environment, endeavour to perform a good flow. In doing so, a dysfunctional voiding may occur, miming a DSD.

16.4
Urodynamic Interpretation in Paediatric Neurological Diseases

Discrete neurological lesions generally affect LUT function in a relatively consistent fashion, according to the area(s) affected, the physiological function of the area(s) and whether the lesion is destructive or irritative. Neurogenic lesions above the brainstem usually cause neurogenic detrusor overactivity with smooth and striate sphincter synergy. Sensation and voluntary striated sphincter function are generally preserved. A non-contractile detrusor may occur either initially or as a permanent dysfunction. In children with NLUTD due to spinal cord disease, the coordination between bladder contraction and sphincter relaxation is most often not preserved. The UDS allows description of four major types of bladder–sphincter dysfunction [13]:

1. Neurogenic detrusor overactivity with sphincter overactivity (i.e. DSD that is the most endangering for the upper tract function)
2. Neurogenic detrusor overactivity with sphincter underactivity
3. Detrusor underactivity with sphincter overactivity
4. Detrusor underactivity with sphincter underactivity

Urinary incontinence due to the underactivity of the sphincteric mechanism is probably the most difficult to treat.

Most NLUTD are encountered in children with myelomeningocele and tethering of the cord or sacral anomalies. About 50% of children with myelomeningocele suffer from DSD, creating functional bladder outlet obstructive neuropathy, exactly in the same way as congenital anatomical urethral observation [15, 16]. Urodynamics are essential in order to define the dysfunctional pattern in lower urinary tract in these children, and to define a therapeutic strategy [10]. Children with pelvic floor overactivity can initiate clean intermittent catheterisation to prevent obstructive neuropathy and preserve renal function. Children with detrusor overactivity can be singled out at a very early age and treated with anticholinergics to avoid detrusor structure damage and preserve bladder capacity and compliance [10].

In children with spina bifida all the above-mentioned bladder–sphincter dysfunctions are possible. More than 40% of patients show DSD with neurogenic detrusor overactivity and sphincter overactivity. Up to 25% of cases present detrusor underactivity with sphincter underactivity. There is a rare possibility to discover detrusor underactivity with sphincter overactivity, and vice versa. A normal lower urinary tract function may be normal in up to 10% of cases. A cystometry and a qualitative EMG are mandatory for an early neurophysiological diagnosis [16]. In children with neurospinal dysraphism after closure of the defect, bladder function may be altered and will continue to change during the first few years of life. As the children grow older, bladder function may again change because of cord tethering. For this reason it is important to keep these children under close surveillance, following them with videourodynamics [16].

Traumatic spinal cord lesions in children are less frequent. During spinal shock detrusor is non-contractile, with a normal bladder compliance, a competent non-relaxing smooth sphincter and a fixed striated sphincter [18]. In some children with incomplete spinal cord lesion and a poor spino-thalamic sensitivity, although there is a reduced or non-specific bladder sensation, the young patients are able to feel involuntary detrusor contractions, complaining of terminal detrusor overactivity incontinence with urgency. These children (often female) may show a suitable movement ability, a good bladder capacity and a less frequent DSD, reaching an apparent normal bladder function. With time, this situation may precipitate leading to a progressive increase in post-void residual and decrease in detrusor contractility. In children with complete traumatic lesions of the spinal cord between level T6 and S2, after they recover from spinal shock, a neurogenic detrusor overactivity occurs together with an absent bladder sensation, smooth sphincter synergy and striated sphincter dyssynergia. Patients with spinal lesions above T6 level may experience smooth sphincter dyssinergia and automonic dysreflexia (a syndrome of exaggerated sympathetic activity in response to stimuli below the level of the lesion). Patient with a spinal cord trauma below S2 usually show a detrusor underactivity with an underactive sphincter [18].

Head trauma in children may cause NLUTD of a minor degree than spinal lesions. This group of patients may complain of urge urinary incontinence, frequency and urgency, and involuntary detrusor contractions may be detected on urodynamic evaluation [7].

Complete or partial sacral agenesis is a rare anomaly occurring as an isolated lesion or in conjunction with imperforate anus, cloacal abnormalities and the so-called syndromes of caudal regression. Most of them have symptoms related to bladder control. Urodynamic findings are extremely variable, ranging from neurogenic detrusor overactivity to non-contractile detrusor, with considerable variation in sphincter EMG activity and synergia [18].

Cerebral palsy is a non-progressive brain injury in the prenatal or perinatal period producing neuromuscular disability and/or specific symptom complexes of cerebral dysfunction. The aetiology is generally infection or a period of hypoxia. These children may display spastic quadriplegia, diplegia or hemiplegia, extrapyramidal choreoathetoid movements, hypotonia with brisk reflexes or a mixed picture of dysfunction. Most of them develop a normal urinary control and only a limited group will be sufficiently intelligent to be truly symptomatic enough to come to urological evaluation. In this group of patients the most common urodynamic observation is neurogenic detrusor overactivity (up to 75% of cases) [13].

Guillain-Barré syndrome is an idiopathic polyradiculoneuropathy characterised by damage at nerve roots and peripheral nerves, frequently following a viral illness. Up to 26% of cases my develop urinary retention or poor bladder emptying. The UDS may show an detrusor underactivity together with neurogenic detrusor overactivity [19].

Some children may show a LUTD without any apparent disease, injury or congenital malformation, in whom a clear neurogenic deficit cannot be demonstrated. According to the definition of the ICCS, this "non-neurogenic bladder dysfunction" can be classified as follows:

1. Overactive bladder syndrome (or urgency syndrome or urgency/frequency syndrome)
2. Dysfunctional voiding
3. Lazy bladder syndrome

In front of this group of patients it is important to make a differential diagnosis with occult spinal dysraphism (anterior meningocele, spina bifida occulta and cystica, lipoma, lipomeningocele, astematomyelia, dermoid cysts and other spinal cord anomalies).

The overactive bladder syndrome is a symptom syndrome characterised by urgency with or without urge incontinence, usually with frequency and nocturia [1]. Classically the symptoms are caused by detrusor overactivity and the child, to minimize wetting, voluntarily contracts pelvic floor muscles and performs other hold manoeuvres, like squatting, to postpone voiding [12]. Urodynamically it is possible to demonstrate involuntary detrusor contractions together with increased electromyographic activity of the pelvic floor muscle during each contraction. The voiding phase is normal, but detrusor contraction during voiding may be extremely powerful [12].

Children with dysfunctional voiding usually present with incontinence, urinary tract infections and constipation. Usually there is a fluctuant or intermittent flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding. In these children there is a poor coordination between detrusor contraction and sphincter relaxation, having similarities with DSD. The voiding is often incomplete with enlarged bladder volumes and unsustained detrusor contractions. The intermittent flow curve pattern is usually indicative, and a combination of post-void residual volume measurement with uroflowmetry and pelvic floor EMG may avoid more invasive UDS. In 1973 Hinman and Bauman described a syndrome as an acquired personality disorder [6], now considered as an extreme end stage of dysfunctional voiding. Urodynamically it is characterised by diminished bladder volume and compliance, detrusor overactivity, and, pelvic floor overactivity during voiding. Videourodynamics usually show all the features of a true neuropathic bladder, and although physical, neurological and instrumental examination may be completely normal, a hidden neurological disorders must be considered [12].

Children with a lazy bladder urodynamically show a bladder greater than normal with a high capacity, normal contraction, an non-contractile detrusor, an intermittent flow and a post-void residual. A correct diagnosis can only be made through urodynamic investigations [12].

16.5
Case Reports

We briefly describe the clinical history and urodynamic findings of four teenaged patients who presented to our department for NLUTD.

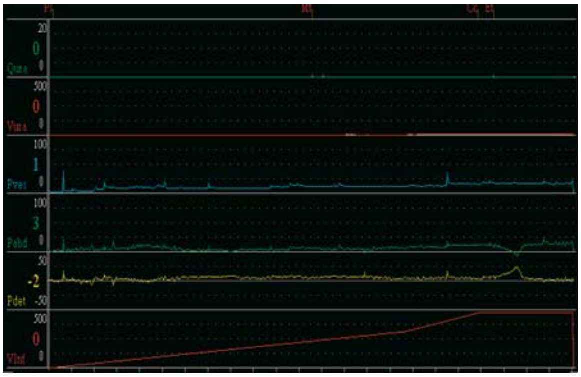
16.5.1
Case 1: Urinary Retention in Girl with Occult Spinal Dysraphism

A 16-year-old girl presented to our department with a long history of complete urinary retention, using intermittent self-catheterisation to void her bladder since she was 14 years old. Physical examination was negative; sacral X-ray showed an incomplete sacral cleft at S1 level and spinal cord MRI documented a slight protrusion of L1–L2 intervertebral disk. Cystometry and pressure/flow study revealed a high maximum cystometric capacity (>500 ml), and a non-contractile detrusor (Fig. 3).

Then a percutaneous nerve evaluation (PNE) test for sacral neuromodulation was performed resulting in the disappearance of urinary retention with a complete restoration of voluntary micturition, urodynamically documented (Fig. 4).

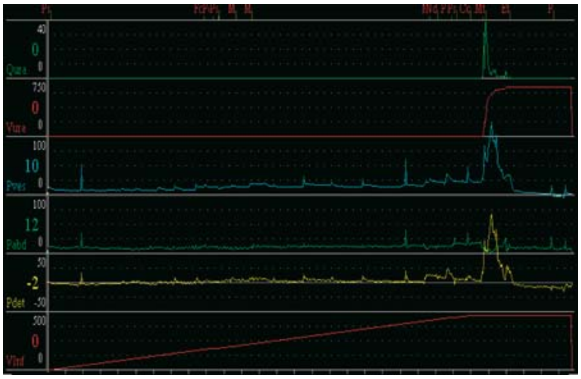
16.5.2
Case 2: Storage and Voiding LUTS in Boy with Lipomeningocele and Tethered Spinal Cord

A 16-year-old boy with cauda equina lipomeningocele and tethered spinal cord surgically treated when he was 5 years presented to our department with a 1-year his-



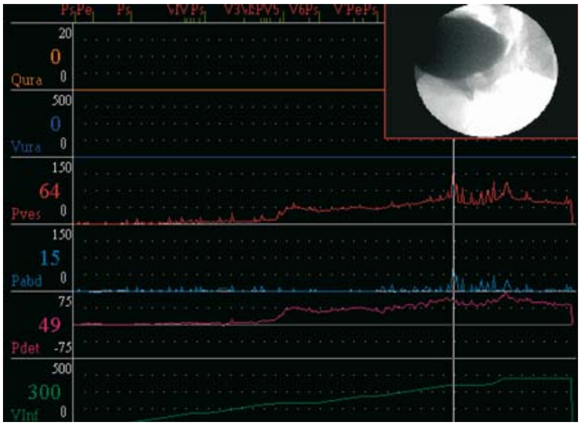
Urodynamic parameter	Value
First sensation of bladder filling	>500 ml^{a}
MCC	>500 ml
Involuntary detrusor contractions	No
PdetQmax^{a}	No^{b}
Qmax^{b}	No^{b}
Urine residual	>500 ml

Fig. 3. Cystometrogram and urodynamic parameters in a girl with occult spinal dysraphism in chronic urinary retention before treatment. MCC maximum cystometric capacity, Pdet Qmax detrusor pressure at maximum flow, Qmax maximum flow rate
[a] Described as flank and suprapubic pain at very large bladder volumes; bladder hyposensitivity [b] Detrusor contractilit



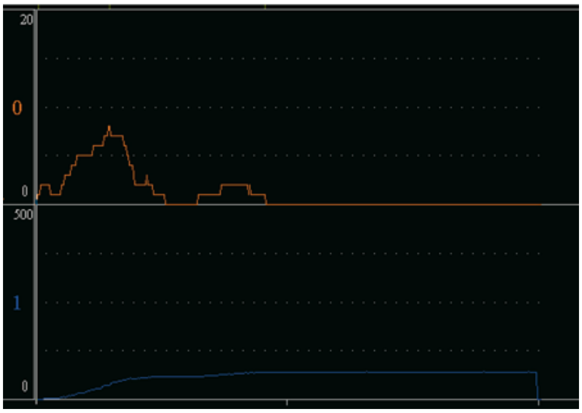
Urodynamic parameter	Value (during PNE stimulation)
First sensation of bladder filling	174 ml
MCC	600 ml
Involuntary detrusor contractions	No
PdetQmax	54 cmH$_2$O
Qmax	33 ml/s
Post-void residual	0 ml

Fig. 4. Cystometrogram and urodynamic parameters after percutaneous nerve evaluation *(PNE)* test



Urodynamic parameter	Description/value
First sensation of bladder filling	80 ml
MCC	700 ml
Involuntary detrusor contractions	Yes (Pdetmax= 60 cmH$_2$O)
Leakage	No
Maximum pressure	75 cmH$_2$O
Qmax	No^{a}
Post-void residual	700 ml

Fig. 5. Videourodynamic findings in a patient with lipomeningocele and tethered spinal cord
[a] Relaxing sphincter obstruction



Uroflowmetry parameter	Value
Flow curve	Intermittent
Maximum flow rate	8 ml/s
Voiding time	0.27 s
Flow time	0.23 s
Average flow rate	3 ml/s
Time to maximum flow rate	0.8 s
Voided volume	70 ml
Post-void residual	350 ml

Fig 6. Uroflowmetry curve and parameters

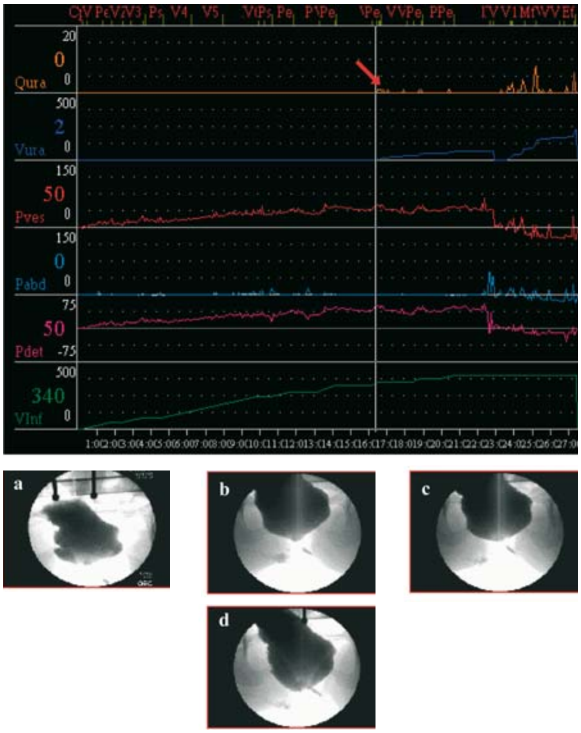
tory of both storage (urgency, frequency, urge incontinence) and voiding (slow and intermittent stream, straining) LUTS.

Videourodynamics showed neurogenic detrusor hyperactivity without incontinence (Fig. 5). The patient was not able to empty the bladder, although he consistently strained to void (radiologically we observed irregular bladder edges, a good bladder neck opening, and a proximal urethral dilatation with a non-relaxing sphincter obstruction). The free urine flow curve was intermittent with very abnormal uroflowmetry parameters and a large post-void residual (Fig. 6).

16.5.3
Case 3: Urinary Incontinence and Incomplete Bladder Emptying in a Girl with Myelomeningocele

A 17-year-old girl with a lumbosacral myelomeningocele surgically treated at birth presented to our department complaining of severe incontinence (>10 pads/die), recurrent urinary tract infections and incomplete bladder emptying. (She had performed intermittent self-catheterisation since she was 14 years, then autonomously she refused to do it anymore.)

Videourodynamics showed neurogenic detrusor overactivity with incontinence, an absent bladder sensation, and a reduced bladder compliance (Fig. 7). The voiding phase was obtained exclusively with Crede manoeuvre. Radiologically we observed a pear-shaped bladder with irregular edges, and pseudo-diverticula. The free urine flow curve was intermittent with abnormal uroflometry parameters and a large post-void residual.

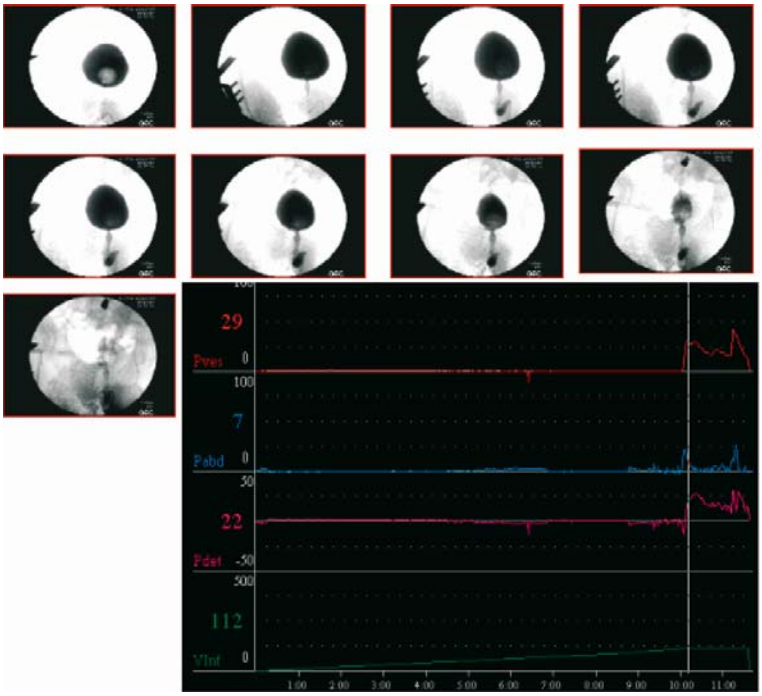


Urodynamic parameter	Description/value
First sensation of bladder filling	No sensation
MCC	360 ml
Involuntary detrusor contractions	Yes (Pdetmax= 50 cmH_2O)
Leakage	Yes
PdetQmax	Not available
Qmax	5 ml/s
Post-void residual	300 ml

Fig. 7. Videourodynamic findings in a patient with myelomeningocele **a**) 50 ml bladder filling, **b**) leakage (red arrow) at involuntary detrusor contraction (detrusor pressure of 50 cmH_2O), **c**) voiding phase, **d**) post void residual

16.5.4
Case 4: Urinary Incontinence, Primary Enuresis, and Urinary Retention in a Spastic Paraparetic Boy

A 15-year-old boy with a history of spastic paraparesis secondary to herpetic encephalitis presented to our



Urodynamic parameter	Value
First sensation of bladder filling	Not available
MCC	110 ml
Involuntary detrusor contractions	Yes (Pdetmax = 34 cm H_2O)
Leakage	Yes (complete bladder emptying)
Urine residual	0 ml

Fig 8. Videourodynamic findings in a patient with spastic paraparesis. Complete radiological imaging of the urethracystographic phase during involuntary bladder emptying

department complaining of urinary incontinence, primary enuresis and a recent episode (1 month before) of acute urine retention, treated with a suprapubic cystostomy.

Videourodynamics showed neurogenic detrusor overactivity resulting in incontinence and complete bladder emptying (Fig. 8). During involuntary detrusor contractions, we observed a good bladder neck opening starting at a detrusor pressure of 16 cmH_2O with a urethra visualization down the external urethral sphincter.

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Electrophysiology

17

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Michèle Mayer

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17.1
Introduction

Electrophysiological tests have been widely used in clinical neurophysiology for over half a century. Regarding the lower genitourinary tract, they were first applied to study the EMG activity of the sphincters and the sacral reflexes and then the afferent and efferent pathways [7]. The genitourinary tract has double innervation: somatic and autonomic nerves are distributed to specific areas of the urinary and genital organs. Whereas the investigation of the sensory and motor somatic nerves is easy and reproducible, testing the autonomic nerves is difficult. Furthermore, most of these tests are not applicable in children because of their invasiveness. We review the methodology of the currently available electrophysiological tests in the pediatric population. These tests are useful for accurately investigating neurourological disorders, such as congenital or acquired spinal cord lesions, in order to determine the level and extent of the neurological damage. Furthermore, they can contribute to the assessment of the spinal and supraspinal control over the lower genitourinary tract. We discuss the specific characteristics of electrophysiological testing in children such as the effect of maturation of the central nervous system during childhood on the latency of the responses. We then evaluate the contribution and relevance of these tests in the pediatric clinical context.

17.2
Electromyography of the External Urethral Sphincter

Electromyography (EMG) records the electrical potentials generated by muscle fibers. Unlike striated muscles, the urethral and anal sphincters show spontaneous electrical activity at rest. During micturition, the urethral sphincter is silent in normal subjects but may show dyssynergic behavior in patients with a suprasacral lesion (i.e., a lesion between the sacral micturition center and the brain stem). The EMG activity of the sphincters (and of the pelvic floor musculature in general) is assessable both physiologically and dynamically during urodynamic investigation, in which case an “integrated” EMG of the sphincters is recorded. It may also be assessed electrophysiologically or analytically during a conventional EMG study.

17.2.1
Dynamic EMG study of the Urethral Sphincter Combined with a Urodynamic Investigation

The EMG study is performed either by inserting a concentric EMG needle electrode into the external urethral sphincter, or by applying surface electrodes to the perianal or perineal skin of children with a normal sensibility. The EMG signal is integrated and rectified to give a global EMG pattern that is recorded throughout the

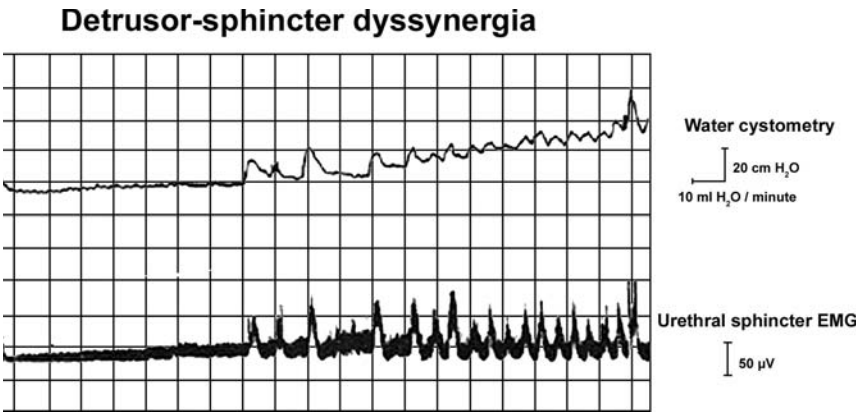

Fig. 1. Detrusor–sphincter dyssynergia (spinal cord lesion). Simultaneous recording of intravesical pressure during filling (urodynamic testing: water cystometry; *upper trace*) and EMG recording of the urethral sphincter (*lower trace*). Notice the "symmetrical" increase of EMG activity with the reflex contractions of the detrusor. This is characteristic of a suprasacral lesion.

urodynamic investigation, i.e., before and during filling of the urinary bladder and during micturition. In normal subjects, there is a gradual increase in EMG activity of the external urethral sphincter (the guarding reflex) during bladder filling, whereas the sphincter is silent during micturition. The EMG activity resumes after micturition. Both the urethral sphincter and the detrusor muscle act synergistically in normal subjects: the urethral sphincter relaxes during detrusor contraction, and vice versa. In case of a suprasacral lesion, the pelvic floor and the detrusor muscle may behave in a dyssynergic way, i.e., both contract simultaneously. By definition, detrusor–sphincter dyssynergia is the concomitant contraction of the urethral sphincter and the detrusor muscle. Because the closure of the urethral sphincter during micturition impedes bladder emptying, it provokes an increase in intravesical pressure, which leads sooner or later to severe alteration of the urinary tract (Fig. 1).

17.2.2
Analytic EMG Study of the Urethral Sphincter

Analytic EMG investigation is performed with a concentric EMG needle electrode (or single-fiber EMG needles) inserted into the urethral sphincter. Few studies have been conducted with normal volunteers, especially in children. Fowler and Fowler have determined reference parameters for the urethral sphincter in adults: normal motor units have a characteristic appearance with duration <6 ms and amplitude between 0.15 and 0.5 mV. Normal units may have up to five turns (phase reversals) [2]. While neurogenic disorders are usually easily identified on the basis of the same criteria as these used in adults (high amplitude and/or polyphasic motor units discharging at an accelerated rate), the identification of myogenic disorders raises major problems, especially because of the difficulty to state that low-amplitude motor units are actually due to myogenic factors, and not merely to needle misplacement.

17.3
Pudendal Somatosensory Evoked Potentials (Pudendal SEPs)

17.3.1
Aim of the Test

Somatosensory evoked potentials (SEPs) consist of a phasic change in the EEG following peripheral nerve stimulation. They provide objective information about the afferent volley in large-diameter fibers from the peripheral nerve to the cortex. Pudendal SEPs were described in the early 1980s. The technique has some limitations: the difficulty of performing a unilateral stimulation of the dorsal nerve (especially in children and in women); the lack of local control of the correct position of the electrode with relation to the nerve; and the small amplitude of the spinal responses [5, 7]; however, by performing dorsal nerve of the penis/clitoris SEPs, one can explore the afferent volley from S4 to the somatosensory cortex. By stimulating the anal margin, one can investigate the totality of the spinal cord. The results of Guérit and Opsomer [4] on electrical brain mapping have validated the use of the C_{z-2} (2 cm behind the central vertex) scalp location for obtaining optimal cortical pudendal SEPs.

17.3.2
Method

Pudendal SEPs are obtained by the electrical stimulation of the dorsal nerve of the penis/clitoris (sensory branch of the pudendal nerve) with the recordings being obtained over the spine and the scalp (C_{z-2}). We first measure the sensory threshold, which, by definition, is the lowest current intensity that gives rise to a perceptible sensation of the electrical current at the point of stimulation. This allows one to determine stimulus intensity at two to three times the sensibility threshold. The number of stimuli is adjusted to get 300–500 artifact-free responses. The spinal response is usually too small in amplitude to be routinely recorded. The cortical response consists of a sequence of positive and negative peaks. The latency of the response is measured both at its onset and at the peak of the first reproducible positivity.

17.3.3
Results

In adult males, the mean latencies of the cortical peaks are, respectively, 35 ms (onset) and 43 ms (P1). Pudendal SEP recording in children raises several problems. Some of these problems are common to the posterior tibial nerve (PTN) and pudendal SEPs; firstly, both are highly sensitive to sedation; secondly, there are currently no real norms, and it is impossible merely to extrapolate from adult data since latencies depend both on the length and the maturation of afferent pathways. The problem is all the more complex as maturation does not follow the same dynamics at the peripheral, spinal-cord, or intracranial levels [1]. Thirdly, there is currently no certainty that pudendal SEPs can be obtained in the youngest children. For instance, we were unable to get them in any patient under 15 months of age, although PTN SEPs were present in some; hence, the well-understandable absence of real norms makes it difficult to differentiate mere immaturity from neurological disorders.

A typical comparative example of PTN and pudendal SEPs is shown in Fig. 2; these were obtained in two young girls, age 15 and 30 months, respectively. In both cases, pudendal cortical responses were present, but of much longer latency and lower amplitude than PTN SEPs.

17.4
Sacral Reflex Latency (Somatico–Somatic Sacral Reflex)

17.4.1
Aim of the test

The sacral reflex latency test examines both sensory and motor branches of the pudendal nerve and their reflex connections in the S2–S4 segments.

17.4.2
Method

The technique consists of stimulating the dorsal nerve of the penis/clitoris and recording the response from the sphincters or the bulbocavernous muscles. The response usually consists of two deflections [6].

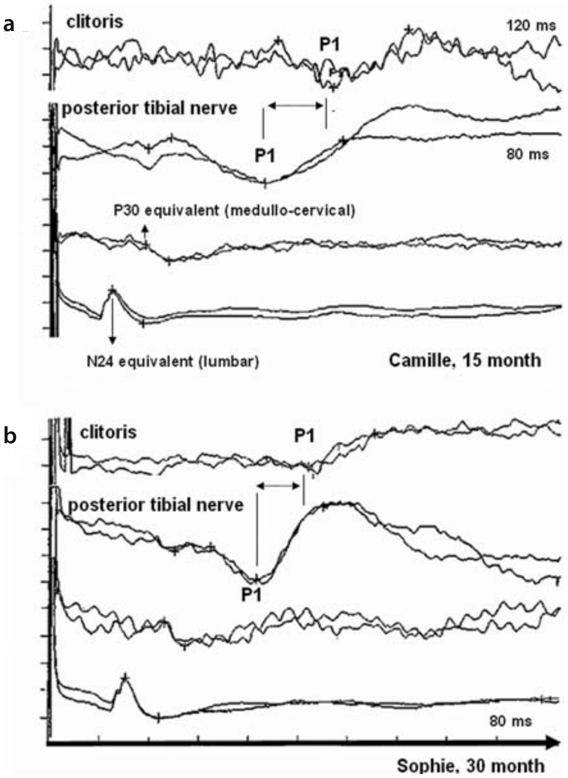

Fig. 2. Comparison between pudendal (clitoridian) and posterior tibial nerve (PTN) somatosensory evoked potentials (SEPs). Recordings obtained in two girls aged 15 months (**a**) and 30 months (**b**), respectively. Posterior tibial nerve (PTN) stimulation gives rise to well-defined lumbar, lemniscal, and cortical SEPs. Cortical SEPs are also well defined upon clitoridian stimulation (*upper traces* both in **a** and **b**), although their amplitude is lower and their latency higher. Note the higher analysis time to clitoridian stimulation in the youngest girl: 120 ms. (Adapted from [3])

17.4.3
Results

In adults, the mean latency of the first deflection (R1) is 31 ms in the bulbocavernosus muscle. A late deflection (R2) is often observed around 60 ms. The difficulty to control needle placement, the contamination by voluntary EMG, and the non-predictive character of the maturation of afferent and efferent pathways accounts for the difficulties in applying these techniques in pediatrics. For obvious ethical reasons, there are currently virtually no pediatric norms.

17.5
Discussion

17.5.1
Indications for Electrophysiological Tests in Pediatric Neurological Disorders

Neurogenic bladder disorders include congenital and acquired dysfunctions of the somatic and autonomic nervous systems that control the lower genitourinary tract (Table 1). Both the extent of the lesions and clinical "picture" are highly variable in congenital neurological abnormalities. For instance, in the tethered cord syndrome, the neurological deficiency is minor at birth and during childhood, whereas it suddenly becomes clinically apparent at puberty, with appearance of neurological, urological, and anorectal symptoms, due to the stretching of the cauda equina. On the other hand, children presenting with a meningomyelocele or sacral agenesis (Fig. 3) usually show overt neurological, cutaneous, bone, ano-rectal, and urinary deficits since birth. In these children with an inborn abnormality, the dysfunction is usually evolutive, thereby requiring a careful evaluation as soon as possible (at birth or when detected) and a close follow-up over the following years; therefore, urodynamic, electrophysiological investigation and imaging are mandatory (Fig. 3). However, due to the inability of these tests to investigate the autonomic nervous system, as well as the difficulty of investigating children, one should carefully select the optimal tests to be actually performed.

17.5.2
What is the Contribution of Electrophysiological Tests in These Children?

17.5.2.1
Electromyography

The specific indications for perineal EMG are twofold: the diagnosis of lower motor-neuron dysfunction and the anatomical localization of muscles.

Lower motor neuron dysfunction should be suspected in the presence of clinical and/or urodynamic signs of dysfunction of the urethral and/or anal sphincters, or with dysraphism. Neurogenic abnormalities are easily identified on the basis of the same criteria as these used in adults.

The anatomical localization of muscles by EMG may be indicated to prove the presence and the quality of innervation of muscle sheets in the presurgical assessment of anal imperforation or, after surgery, in the event of remaining functional problems (incontinence or retention).

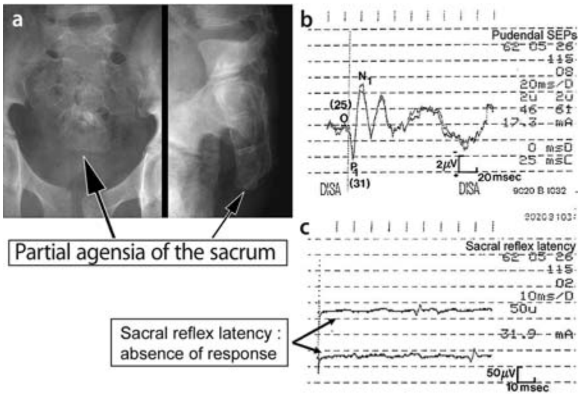
a
Partial agensia of the sacrum
b
Pudendal SEPs
N1
(25)
(31)
P1
2µV
20msec
DISA
c
Sacral reflex latency
Sacral reflex latency : absence of response
50µV
10msec

Fig. 3. Partial sacral agenesia. a X ray film of the sacrum (frontal and lateral views) shows the bone defect. **b** Somatosensory evoked potentials: normal tracing with respect with the height of the patient. **c** Sacral reflex latency: no response in the external urethral sphincter

Table 1. Indications of electrophysiological tests in paediatric pathology

1. Congenital disorders
• Morphological – Anatomical : – bladder exstrophy – anal imperforation • Spinal abnormalities : – meningomyelocele – sacral agenesis – tethered cord syndrome
2. Acquired disorders
• Trauma • Tumors • Viral and metabolic disorders

17.5.2.2
Somatosensory Evoked Potentials

Theoretically, the specific interest of pudendal, when compared with PTN, SEPs is for the assessment of the most distal part of the conus terminalis, of the fibers of the cauda equina that correspond to the lower sacral levels, and of the pudendal nerve itself; hence, several neuropediatric disorders may be associated with a specific involvement of these structures: sphincter dysfunction of malformative (perineal or spinal) or traumatic origin; sexual ambiguities; inflammatory disorders; or tumors. However, there is a dramatic discrepancy between the potential usefulness of pudendal SEPs in children and the paucity of literature data, the main reason for which is likely to be the aforementioned methodological difficulties. This precludes any retrospective study of the specific interest of pudendal nerve SEPs in children.

17.5.3.2
Sacral Reflex Latencies

One would expect sacral reflex latency to be useful for indirectly investigating the integrity of the micturition reflex. In practice, however, the aforementioned methodological pitfalls make it difficult to apply this technique in pediatrics. While useful information can be obtained for well-structured responses, the absence of a response must be interpreted with the greatest caution. This technique does provide information on the functionality of the pelvic floor muscles, including the urethral sphincter. This test is useful in the investigation of continence problems as well as sexual (ejaculatory) disorders in adults.

17.6
Conclusion

Genitourinary electrophysiological tests are of some interest in the evaluation of the innervation of the pelvic organs, but their indications in the pediatric population are currently limited. As mentioned previously, the contribution of the somatic nerves to the innervation and the physiology of the lower genitourinary tract is limited compared with that of the autonomic nerves; however, from a technical point of view, the somatic nerves are easily accessible while the evaluation of the autonomic genitourinary pathways is invasive and therefore not well accepted by the patients, which explains why most authors rely exclusively on the testing of the somatic nerves. This might lead to simplistic and erroneous conclusions. For instance, after radical surgery of the pelvis for cancer, patients may have bladder areflexia due to *autonomic* denervation, while the somatic innervation to the penile skin or the pelvic floor musculature remains intact.

In this respect, the evaluation of the motor-somatic tracts might look more interesting since the motor branch of the pudendal nerve controls the pelvic floor musculature, including the anal and the urethral sphincters; hence, both muscles are directly involved in the mechanisms of anal and urinary continence and the ischio- and bulbo-cavernosus muscles are responsible for the prograde expulsion of the sperm during sexual activity. Such evaluation can be obtained through magnetic stimulation of the cerebral cortex or the spinal cord . Further studies are needed to assess its feasibility, the effect of maturation, and clinical usefulness in children.

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Endoscopy

18

Prasad Godbole · Ewen A. MacKinnon

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18.1
Introduction

The bladder serves two important functions, namely storage of urine (reservoir) and timely and complete emptying. Normal bladder function involves a complex coordinated interaction between the detrusor muscle, the striated sphincter muscle complex and neural control from the sympathetic and parasympathetic pathways and the higher centres. Disruption in the neural regulatory process can result in neuropathic bladder dysfunction. This chapter highlights the various types of neuropathic bladder dysfunction and the role of endoscopy in such cases.

18.2
Aetiology and Classification

Neuropathic bladder dysfunction can occur as a result of disturbance in detrusor function, sphincteric function or a combination of both.

The detrusor can be hypercontractile, hypo- or noncontractile, normal, or hyperreflexic in nature. Changes in detrusor function may affect compliance.

The sphincter complex may demonstrate (a) inherent sphincter weakness or (b) a hypertonic sphincter.

A combination of disturbance in detrusor function and sphincter complex may lead to detrusor sphincter dyssynergia (DSD).

Management of children with neuropathic bladder dysfunction is based on the following principles: (a) protection of renal units by ensuring a reservoir that is low pressure, compliant and emptied at regular intervals; (b) achieving social continence, both urinary and fecal; and (c) prevention of urinary tract sepsis.

Investigations of neuropathic bladder dysfunction should include periodic ultrasound monitoring of the upper tracts, a baseline cystourethrogram and functional study, and a full urodynamic assessment. The urodynamic assessment should include a full and detailed history and clinical examination including sensory level, bladder assessment using frequency-volume charts, and bladder scanning and formal invasive urodynamics.

18.3
Endoscopy

The mainstay of managing children with neuropathic bladder dysfunction remains clean intermittent catheterisation, anticholinergics and chemoprophylaxis as indicated. The role of endoscopy is thus somewhat limited but increasingly is finding more applications, which are discussed herein.

18.3.1
Urethra

18.3.1.1
Endourethral Injection of Bulking Agents

Endoscopic endourethral injection of bulking agents for urinary incontinence in children with neuropathic bladder dysfunction has been reported with variable results

[1–4]. The authors reported on their experience of endourethral injection of bulking agents in 14 children with neurogenic bladder dysfunction [5]. All patients had a compliant stable low-pressure bladder with sphincteric weakness. The technique consists of an endourethral submucosal injection of the bulking agent into four or more points at the junction of the bladder neck and posterior urethra to obtain visual occlusion of the lumen. A suprapubic approach with endoscopic control has been described by Abel and Gough [6]. Our experience was contrary to previously published series. We found that after an initial short-term benefit, in the long term this technique was unreliable and ineffective.

18.3.1.2
Sphincteric Injection of Botulinum Toxin A

This technique has been well described in the literature on adults [7–9]. In carefully selected cases of children with detrusor–sphincter dyssynergia, injection of botulinum toxin A may play a role in improving bladder emptying. In the authors' experience, the effect lasts for up to 6 months and may be repeated.

18.3.2
Bladder

18.3.2.1
Insertion of Suprapubic Catheters for Urodynamics

Cystoscopic control of suprapubic catheter insertion can help in correct placement and can be used when any concomitant diagnostic/therapeutic procedure is being considered in children with neuropathic bladder dysfunction.

18.3.2.2
STING for Vesicoureteric Reflux

Vesicoureteric reflux in children with neuropathic bladder dysfunction is a major cause of morbidity [10]. In cases where intermittent catheterisation, anticholinergics and chemoprophylaxis fails to prevent breakthrough infections, correction of the reflux can be considered. Open ureteric reimplantation may be technically difficult in the thick-walled bladder. Subureteric injection of teflon may be an alternative, and variable success rates have been reported [11–14]. Difficulty in identifying the ureteric orifices has been described in the trabeculated bladder [15].

In the authors' opinion, correction of the vesicoureteric reflux should be reserved for those children with a stable low-pressure compliant bladder who have recurrent breakthrough infections and upper tract deterioration. Some children with a high-pressure bladder not responsive to conventional therapy may be candidates for urinary tract diversion or an augmentation cystoplasty, rather than correction of the reflux per se.

18.3.2.3
Detrusor Injection of Botulinum Toxin A

This technique may be considered in the hypertonic/hyperreflexic neuropathic bladder unresponsive to conventional treatment. Although well described in adults [16–18], it has not been extensively used in children and hence experience is limited.

18.3.2.4
Endoscopic Retrieval of Calculi in the Neuropathic Bladder

The risk of calculi in the neuropathic bladder, especially after augmentation, is well documented [19–21]. Traditionally, open surgery has been the technique of choice to achieve complete removal of the calculi. Minimally invasive techniques using laparoscopic entrapment sacs or laser/electrohydraulic lithotripsy have been described [22, 23]. At times, stones may be removed with a traditional stone basket, either urethrally or via a Mitrofanoff stoma.

18.3.2.5
Laparoscopic-Assisted Reconstructive Procedures

Laparoscopic-assisted reconstructive procedures, including augmentation, catheterisable conduits and ACE conduit formation, have been described [24–26]. It has been suggested that these techniques confer the benefit of less postoperative discomfort and adhesion formation and cosmesis. Experience in these techniques is, however, limited. In the authors' experience in younger children, an augmentation cystoplasty, Mitrofanoff and ACE can be performed through a cosmetic short Pfannenstiel incision with the same advantages.

18.3.3
Kidney

18.3.3.1
Laparoscopic Nephrectomy: Retroperitoneal or Transperitoneal?

In children with a non- or poorly functioning kidney and recurrent infections, or where it is associated with a dilated ureter suitable for ureterocystoplasty, the laparoscopic approach to nephrectomy can be considered. This may be accomplished by either the retro- or transperitoneal route with minimum morbidity. In the authors' experience, the retroperitoneal route is technically more demanding but should be the technique of choice where possible. Technical details of the procedure have been described in several excellent texts [27, 28].

18.3.3.2
Surveillance After Reconstructive Surgery

Development of malignancy along the anastomotic line following bladder augmentations has been described in case reports and experimental studies highlighting the needing for periodic surveillance and biopsies [29–31].

18.4
Conclusion

In conclusion, endoscopy plays a limited role in children with neuropathic bladder dysfunction. With improvement in technology, however, it may play a bigger role in the management of these children.

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Simplified Approach and Practical Classification

19

Jean-Michel Guys

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19.1
Introduction

Regardless of etiology, neurologic bladder usually leads to alterations in urine storage and bladder–sphincter synergy. Excessive contraction of the detrusor muscle, which often fails to respond to the inhibitory action of the pontine and suprapontine centers, creates a high-pressure syndrome. Muscle hypertrophy, followed by muscle deterioration due to fibrosis and chronic infection, inevitably reduces bladder capacity. The vesicoureteral junction is highly exposed to deterioration (megaureter due to, or secondary to, reflux), and the resulting chronic infection often leads to alterations in the upper tract. The striated urethral sphincter becomes spastic in most cases.

This natural course explains why most cases of neurologic bladder, whose most common clinical manifestation is urinary incontinence, involve obstruction of the lower tract due to major bladder–sphincter dyssynergia. Spontaneous improvement is never observed.

Urinary incontinence is then only a symptom that may correspond to a wide variety of situations including:

1. Normal bladder (Fig. 1a) in association with true sphincter incompetence (rare).
2. Undersized bladder (Fig. 1b) limiting urine storage time and requiring frequent voiding (incompatible with a normal lifestyle).
3. Oversized underactive bladder (Fig. 1c) that voids due to overfilling.

Any of these situations can occur in association with sphincter dysfunction (S=0/+/-) that can also have a variety of causes ranging from hypertonic obstruction to total absence of resistance, but always leads to the same clinical manifestation, i.e., leakage. Careful paraclinical investigation as described elsewhere in this volume is necessary to determine the exact cause of this clinical symptom.

19.2
Role of the Paraclinical Investigation

For all types of neurologic bladder, radiographic and urodynamic studies are necessary to determine the morphological and functional status of the upper tract, and the competency of the lower tract, in performing its three functions, i.e., storage, voiding, and synergy between the two. Analysis of each abnormality, in sequential order, is essential for therapeutic decision-making.

Preclinical investigation requires special medical facilities and examination conditions that have a variable but almost inevitable effect on patient psychology, especially in children. This problem explains the need for careful interpretation of findings and for comparing examination findings with clinical or endoscopic data. Examinations should be repeated, if necessary, due to poor patient cooperation (frequent in children) and problems secondary to associated physical challenges (e.g., orthopedic problems).

The upper urinary tract should be studied using ultrasonography, with or without CT scan, or more recent technologies such as MRI and isotope scanning. Ultrasonography may be sufficient at the early stages of the disorder, since the kidneys are usually not affected, especially in patients with congenital neurologic bladder; however, functional testing is mandatory if pyelonephritic renal scarring is suspected. Since the main goal of therapy in children is to preserve renal function, these examinations should be repeated regularly and therapeutic strategies should be adapted depending on the findings.

The most important radiographic examination for investigation of the bladder is cystography in association with urodynamic study. This combination allows thorough functional and dynamic morphological assessment of the lower urinary tract.

Cystography is usually performed by the retrograde route. Some characteristics must be pointed out in the

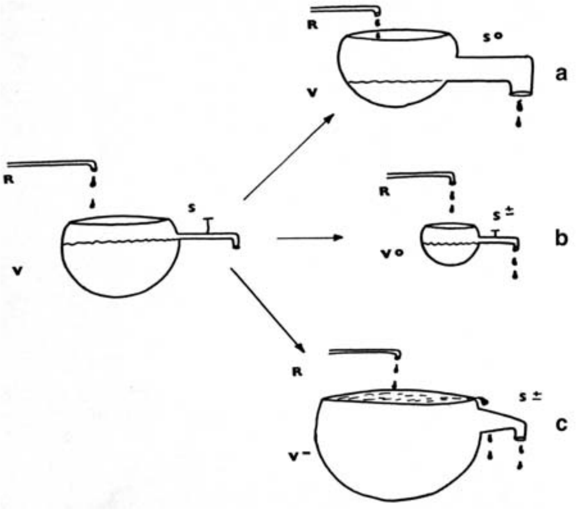

Fig. 1. **a** Normal bladder. **b** Undersized bladder. **c** Oversized, underactive bladder

child: urethral catheters must be chosen to allow micturition during the examination. Determination of the total functional capacity of the bladder is mandatory for therapeutic decision making. In patients with major loss of sphincter resistance, introduction of an occlusive catheter into the bladder neck allows more accurate assessment of bladder capacity and of the response of the detrusor muscle to increasing intravesical pressure.

Bladder pressure data are useful for classifying neurologic bladder. Dynamic electromyography of the striated urethral sphincter may be the only means of visualizing bladder–sphincter dyssynergia, since recordings from the anal sphincter or another perineal muscle are often uncorrelated with the striated urethral sphincter; however, the value of specific analysis has not been validated in children. Sphincter resistance must be carefully measured. Determination of leak-point pressure during bladder pressure testing is much more useful than theoretical study of the pressure profile classically obtained in the adults.

Additional testing of somesthesic evoked potentials can be performed to measure peripheral and central, sensory and motor, nerve pathways. Perineal evoked potentials are easily measurable after stimulation of the dorsal nerve of the penis or clitoris. These findings can be particularly useful if clinical assessment of sensitivity is difficult. Motor evoked potentials may be useful to evaluate the integrity of the nerve pathways underlying bladder–sphincter control; however, these techniques require specialized equipment and are needed only insofar as required to ascertain that manifestations are of neurologic origin in difficult cases.

The main goals of paraclinical work-up are to assess the risk for upper tract deterioration, identify situations that might induce deterioration of the bladder, and to evaluate the result of therapeutic intervention.

For therapeutic purposes it seems much more useful to know if micturition can be controlled voluntarily, occurs at low pressure, and is complete rather, than to classify the bladder manifestation according to standard neurologic categories, i.e., central, peripheral, or mixed. For this reason, it is essential to study the three bladder functions, i.e., storage, retention, and voiding. In the present author's opinion, the functional urologic classification described by Wein is the most informative system for therapeutic decision making.

Urinary incontinence in itself cannot be considered as an independent prognostic factor. The most useful urodynamic prognostic factor is leak-point pressure, since it depends on both bladder compliance, functional capacity, and sphincter resistance. The critical cutoff value has been estimated to be 40 cmH_2O. Another unfavorable prognostic factor is bladder hyperactivity occurring early during filling with peaks again regularly reaching 40 cmH_2O or, in addition, a continuous high-pressure range during bladder filling again higher than 40 cmH_2O.

Finally, in association with high pressure, poor bladder voiding, whether due to dyssynergia or hypertonic sphincter, worsens the high-pressure syndrome. From a clinical standpoint the most important prognostic factor is chronic urinary retention in the bladder.

19.3
Treatment

The main goal of treatment of micturition disorders associated with neurologic bladder is to protect the upper urinary tract. In older children (starting primary school or entering middle school), treatment of incontinence becomes a social necessity.

Normal urinary continence is defined as a period of 4 h without leakage between micturition.

The main steps of the treatment of neurologic bladder are as follows:

1. To ensure emptying of the bladder (voluntary and complete)
2. To improve bladder capacity (low-pressure filling, good compliance)
3. To increase sphincter resistance (in coordination with bladder voiding in order to assure bladder storage)

We must be aware for each patient to "balance" the different surgical or medical procedures in order not only to treat the urinary incontinence, but also to take care of the digestive, orthopedic, and sexual problems which can be associated.

The strategies for achieving these goals are discussed elsewhere in this volume.

Clean Intermittent Catheterization

20

Mario Lima · Francesco P. Di Lorenzo
Paolo Messina · Laura Greco

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20.1
Introduction

In patients affected by Neurogenic Bladder Dysfunctions (NBD), infrequent or incomplete voiding, thickness of the bladder wall and increased urethral resistance are risk factors for urinary tract infections as well as continence and urinary tract anomalies (ureteral meatal entrapment, vesico-ureteral reflux). A large majority of patients achieve an alleviation of the NBD symptoms with Clean Intermittent Catheterization (CIC). Physicians and urotherapists, in order to achieve an effective treatment, should obtain a correct diagnostic classification of the vesico-sphincteric dysfunction. Firstly, it is important to identify whether the problem lies in the filling phase or in the emptying phase of the bladder. Then, it is necessary to select all the possible therapeutic options, which change according to whether the problem is related to the bladder, the urethral resistances, or both. One of the obvious pitfalls of reflex evaluation and treatment is that we might ignore a potentially reversible reason for this dysfunction. The etiology of a particular voiding dysfunction and its potential reversibility should always be considered.

20.2
Historical Outline

Vesical catheterism was, without any doubt, one of the first therapeutic acts. It was certainly performed also in ancient times. The Ancient Chinese wrote about the use of onion stalks. The Sushruta Samhita, an early Indian surgical text dated approximately 1000 B.C., describes the use of golden, silver, iron and wooden tubes, for urine evacuation, urethral strictures, instillation of medication in the bladder, and assistance in lithotomy. Hippocrates (460 to 377 B.C.), whose writings on vesical lithiasis have come to us, certainly used catheterism on his patients. The claim that the Greek anatomist Erasistratus (310 to 250 B.C.) invented the catheter in Alexandria is unsubstantiated and unlikely [1].

De Medicina, written in Latin in approximately 30 B. C. by Celsus Aurelius Cornelius, describes surgical instruments and gives instructions for catheterization in case of urinary retention. The excavation of the city of Pompei, buried in 79 B.C. by the eruption of Mount Vesuvius, revealed in a surgeon's house a variety of bronze urethral catheters. Rufus of Ephesus (circa 100 B.C.), who practiced in Alexandria, wrote "Diseases of the Kidney and Bladder," perhaps the first specific urological treatise. He observed that a paralytic bladder, for example from spinal cord injury, should be treated by catheterization. Paulus of Aegineta, the last great Byzantine physician, left precise instructions on intermittent catheterization in "Seven Books on Surgery."

Avicenna (980–1037), a Saracen philosopher, scientist, physician, and Koranic scholar, coordinated Hippocratic and Galenic concepts with contemporary medical practice and Islamic principles. He advised that catheterization should be performed gently and without force, using soft cheese as a lubricant, and warned against catheterization when a bladder was inflamed. Rhazes (Abu Bakr Muhammad ibn Zakaria, 865–925), an influential Persian physician, has been credited with the use of side holes in a catheter.

Friar Theodoric of Lucca (1205–1298) produced a Latin surgical text around 1267 that described catheterization with reference to the management of bladder stones. The drawings in Armamentarium Chirurgicum (Fig. 1), by the German surgeon Scultetus of Ulm (1666), are to be considered some of the earliest illustrations of catheterization. Morgagni (1682–1771), the great anatomist of Padua, earned much of his reputation by relating clinical problems to pathological conditions. He described specific situations in which catheterization might be unsuccessful. Since then, historical references have become increasingly more frequent.

Industrialization improved the manufacturing ability to make better surgical instruments and the scientific means to fit the tool to the task. Amussat (1796–1856) was one of the first of many great French catheter experts. Jean Civiale (1792–1867) created the urological service at the Necker Hospital in Paris, the source of great advances in urethral instrumentation and technique. The Goodyear patent for moldable hard rubber in 1851 permitted a faster and cheaper production of catheters. Auguste Nélaton (1807–1873), physician to Napoleon III, introduced a flexible rubber catheter in 1860. In the same period, Charrière (1803–1876), a Parisian instrument maker, developed a sizing system that became known as the French scale.

By the late nineteenth century a wide armamentarium of catheters was available to the practitioner. George Tiemann's catalogue of surgical instruments listed nearly 80 different types of catheters. In 1885 August Rüsch established a firm to produce medical instruments, especially catheters.

The weapons and wars of the twentieth century have altered medical practice by producing an unprecedented number of spinal cord ballistic injuries. The concomitant bladder dysfunction was considered to be an appropriate indication for urethral catheterization. In June 1935, Frederick E.B. Foley (1891–1966) introduced a rubber balloon catheter, an in-dwelling hemostatic device that could be held in place by its own configuration. In 1946 Guttmann, one of the first specialists in spinal cord injury, recognized the dangers of bladder overdistention and saw that drainage of the areflexic bladder was mandatory for survival. He noted that sterile intermittent catheterization was preferable to chronic intubation.

Jack Lapides (Fig. 2) first introduced clean (non-sterile) intermittent catheterization in 1970. He and his nurse, Betty S. Lowe, first applied the clean intermittent self-catheterization technique in a 30-year-old woman with diurnal incontinence and recurrent urinary tract infections secondary to a neurogenic bladder from multiple sclerosis [1]. The recognition that sterility of the catheter was unimportant was provided by the patient herself: she once dropped the catheter on the floor and, unable to resterilize it, simply proceeded with her catheterization with no ill effects. Undaunted by criticism, Lapides expanded the clean intermittent catheterization program to other patients with NBD, including men and children. The merits of Lapides' concepts and clean intermittent self-catheterization have been justified for

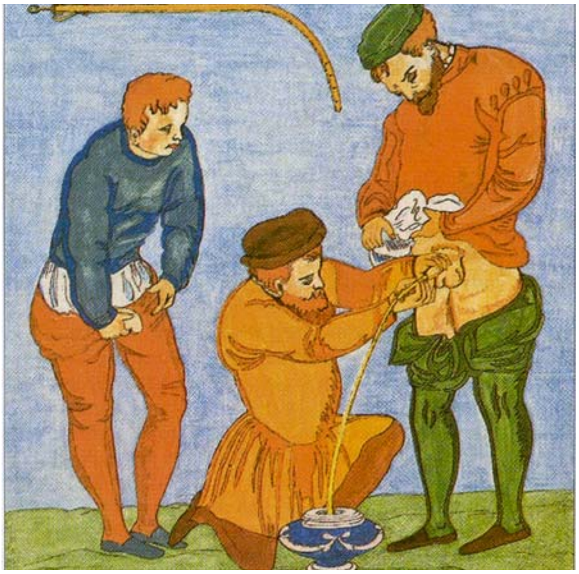


Fig. 1. The *Armamentarium Chirurgicum*, the first iconographic representation of catheterization

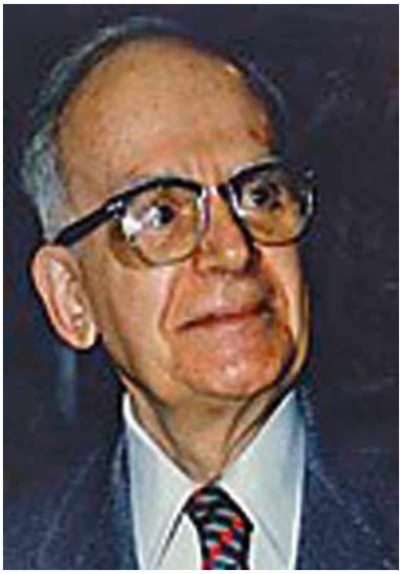


Fig. 2. Jack Lapides

more than three decades of subsequent worldwide experience.

20.3
Indications

In patients with a verified diagnosis of NBD, before choosing the therapeutic treatment, it is important to characterize, by means of urodynamic, radiological and ultrasound studies, the type of dysfunction in order to single out those patients with bladder at risk for renal function. Some authors suggest, in this case, to start CIC in the newborn period or early in infancy [2]. It is essential to consider the vesical component and the sphincteric component [3]. The storage capacity can be compromised, both in a lazy bladder and in the detrusor hyperactivity. During the spontaneous voiding phase, it is important to determine the type of sphincteric alteration: atony or hyperactivity. Among the different possibilities, doubtlessly the most serious one regards the high vesical pressures with thickness of the bladder wall, associated with high sphincteric resistances. In this case, CIC associated with anti-cholinergic drugs, is well indicated. On the other hand, in the presence of an incapacity to completely empty the bladder and, thus, of a post-voiding residual, with recurrent urinary infections, CIC finds its indication. In the sphincteric insufficiency with normal bladder compliance, CIC with or without endoscopic procedures, can improve the continence; therefore, the main indications for CIC in pediatric patients with NBD are as follows:

1. Treatment of complications on the upper urinary tract (reflux, dilation)
2. Control of recurrent symptomatic infections and prevention of urological complications in bladder "at risk"
3. Control of urinary incontinence

20.4
Training

After giving the therapeutic indication, it is advisable to evaluate the suitability of CIC. The psycho-social compliance of the family, the ability of the patient in case of self-catheterization, and the presence of serious sensorial and motor handicap must be considered. The psychological approach with the parents and the pediatric patient (when over 3 years of age) requires the urotherapist (physician-supporting figure) to motivate the parents [4, 5], to help them to accept CIC as a non-traumatic, invasive, but indispensable procedure. It is important to tranquillize parents and patients, to assuage their doubts and fears, and to teach them anatomy. It must be clear that CIC does not interfere with the possibility of acquiring spontaneous micturition.

After a theoretical explanation of the CIC technique, it is possible to proceed with the field experience (Fig. 3). Parents must be supported until mastery is obtained. Generally, this first phase requires a trial period of a couple of days; afterwards, it is necessary to check after about 1 month.

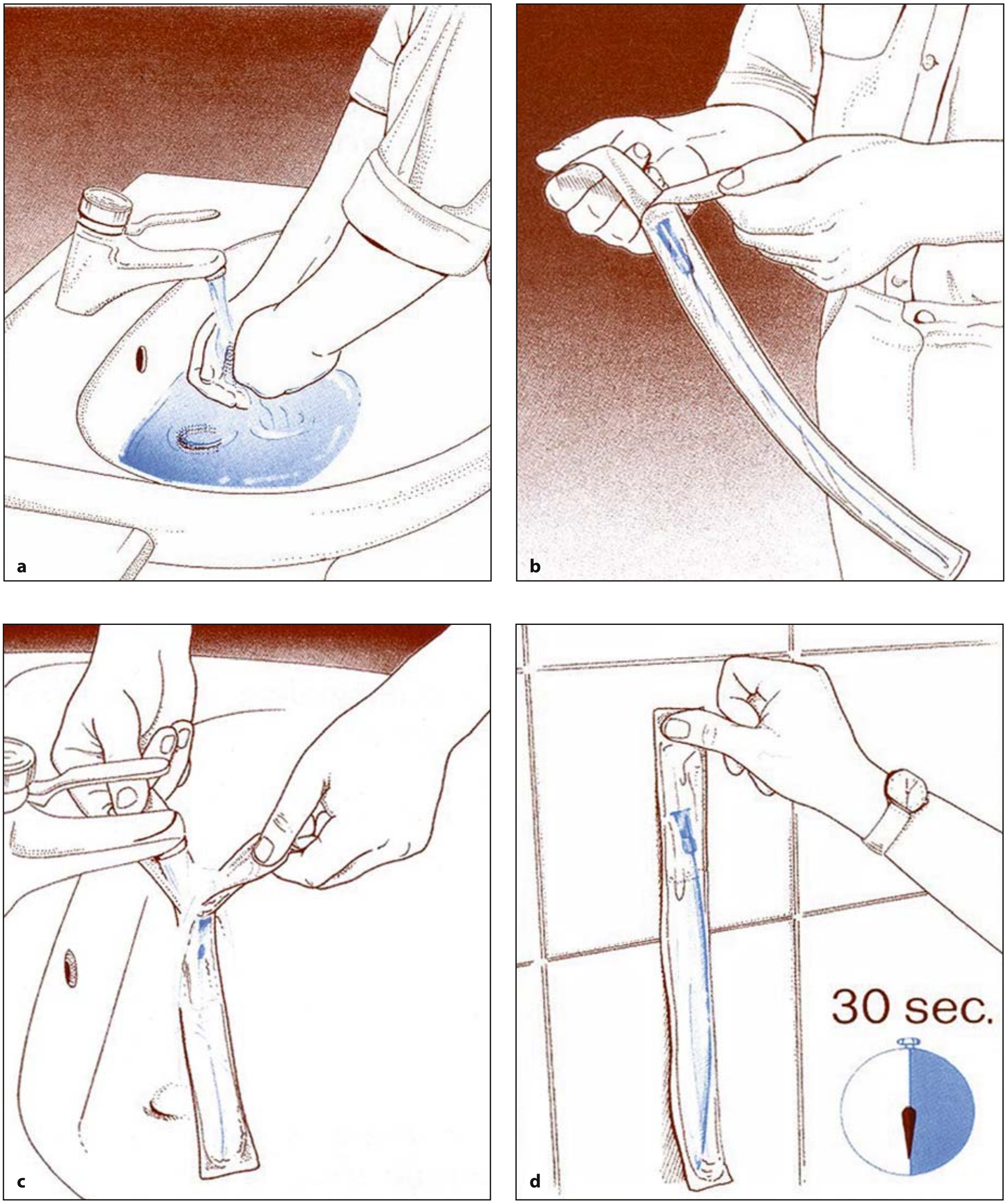
Children over 4–5 years of age can learn self-catheterization quite easily [2, 6]. Introducing CIC at a young age provides the child with the opportunity to develop a positive attitude towards his or her body, and to build self-esteem. Trust must develop between the child and the "teacher" (physician or nurse). The child needs step-by-step instruction and guidance during catheter insertion and removal. The most critical part of the training is to be able to locate the meatus, which is more difficult for girls. Repeated failure to locate the meatus can destroy the child's confidence in mastering this skill. It is useful to start from visualizing the genital anatomy. In girls, a mirror should be used to visualize the anatomical position of the urinary meatus. Then, the sense of touch is used to maintain the skill: a finger is placed over the urethral meatus, then replaced by the tip of the catheter. Anatomic drawings and videotapes of other children can be shown in order to give rise to new questions. At the same time, it is important to explain why catheterization is needed. The time frame for doing this depends on the child's ability.

Children who have been catheterized since infancy learn to self-catheterize by the age of 4 or 5 years. The transition to self-catheterization may take up to 2 years depending on the child's mental and physical development. It is much more difficult to teach children who have not been previously catheterized, and they often require a period in hospital for an intensive CIC teaching program.

The same tools can be used to teach self-catheterization to adolescents, but with a more detailed emphasis on explaining the reasons for CIC as part of the educational process. In addition, independence and separation from the parents can become significant issues for the adolescent.

The CIC must be performed at least four times a day. To obtain good results it is important to empty the bladder every 3 hours. The emptying is in fact one of the most important weapons against infections [7]. To control incontinence a higher number of catheterizations per day may be necessary; however, every patient is a single case and must be considered as part of the whole.

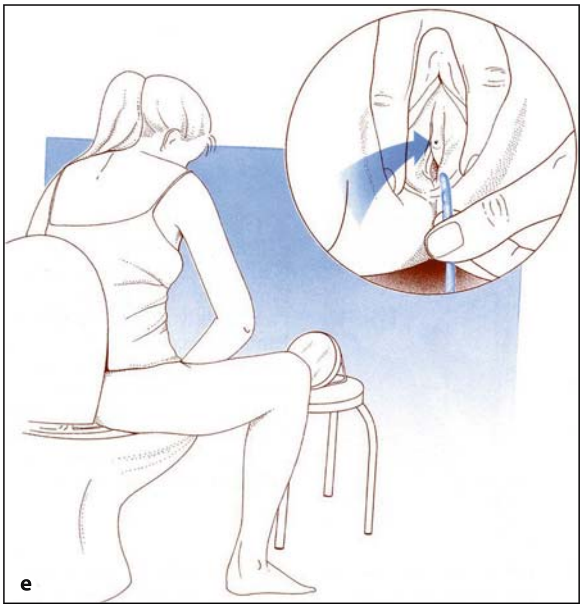
A periodic urodynamic re-evaluation every 6 months is recommended. This re-evaluation is easier for both parents and physician if helped by a "Diary of CIC"

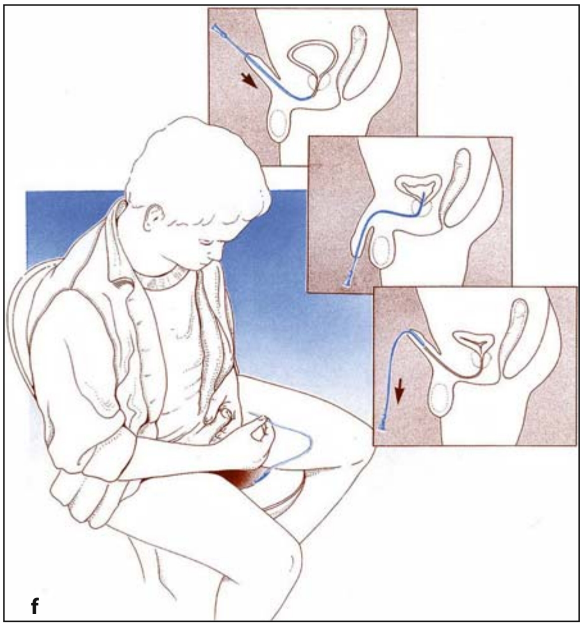


(Fig. 4). In this diary, the parents must record the timing of "micturitions," quantity of urine evacuated, postvoiding residual when CIC is performed after a spontaneous micturition, type of incontinence, and dry interval between CIC. Other annotations, such as fever, therapies, and urine macroscopic features (smell, color, hematuria), can be added.

20.5
Materials

Since the worldwide diffusion of CIC in the pediatric age, there has been a big evolution in the materials used for the catheterization. At the beginning, catheters made of metal or rubber were used. Then, synthetic materials





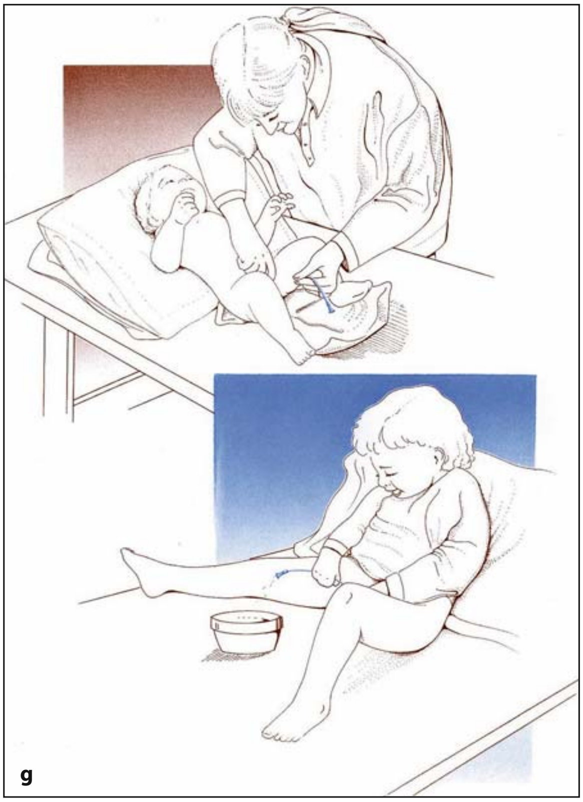
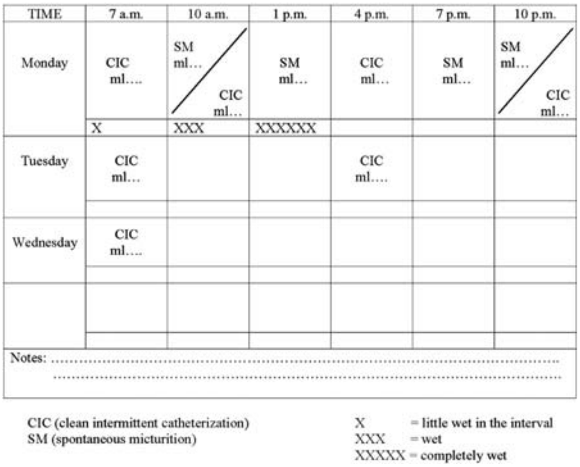


Fig. 3. Instructions on how to perform a clean intermittent catheterization. **a** Accurate hand washing. **b–d** Preparation of the pre-lubricated catheter: only 30 seconds soaked in water are needed to create a slippery surface on the catheter. **e** Self-catheterization in a female. **f** Self-catheterization in a male. **g** Catheterization performed by a parent and self-catheterization in an older child

were introduced; however, catheters could be sterilized and reused. They were generally kept in a bottle with a disinfectant. Then, disposable silicone catheters were introduced, which had to be lubricated before use. Generally, the lubricant was a jelly, sometimes containing anesthetic or antibiotics. Only a few years ago, disposable pre-lubricated catheters came on the market [8]. These disposable sterile plastic (polyvinyl chloride) catheters (Fig. 5) are coated with a nonreactive hydrophilic polymer, polyvinylpyrrolidone, with sodium chloride crystals to raise the osmolarity and enhance the water-binding ability. Soaked in water, the polyvinylpyrrolidone chains bind the lubricating liquid with approximately the same osmolarity that there is in the urethral epithelium; thus, a greatly decreased friction between the catheter and urethral mucosa is achieved by a contact area which consists mainly of water molecules. The friction of this catheter is about ten times less than that of a catheter lubricated with chlorhexidine jelly [9, 10]. More recently, it has been possible to find on the market prepackaged kits, with sterile saline and urine collecting bags.

Before performing CIC, it is necessary to disinfect accurately hands and genitalia. Local disinfectants are usually not aggressive. Jelly and ointments are more often sterile and disposable.

Endovesical catheters permit local therapies, which are currently preferred over the systemic ones [11].



TIME	7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.	10 p.m.
Monday	CIC ml....	SM ml… CIC ml…	SM ml…	CIC ml…	SM ml…	SM ml… CIC ml…
	X	XXX	XXXXXX			
Tuesday	CIC ml…			CIC ml....		
Wednesday	CIC ml....					

Notes: ………………………………………………………………………………………
………………………………………………………………………………………

CIC (clean intermittent catheterization)
SM (spontaneous micturition)

X = little wet in the interval
XXX = wet
XXXXX = completely wet

Fig. 4. Diary of clean intermittent catheterization

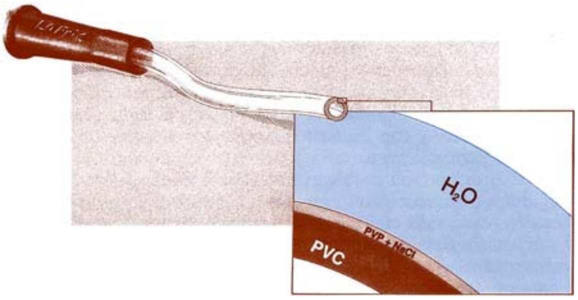


Fig. 5. Structure of a pre-lubricated hydrophilic disposable catheter

20.6 Complementary Treatment

20.6.1 Pharmacotherapy

Pharmacological therapies, both occasional and continuative, can be added to CIC. It is preferable, if possible, to give drugs directly into the bladder, through the catheter.

It is not necessary to associate prophilactic treatment, although it was suggested in the past, at present, it is preferable to treat acute infections. Concerning bacteriuria, it is possible to keep the microbial load low with cranberry juice [12], hydration, and a regular frequency of "micturition"; however, if necessary, it is possible to give antibiotics endovesically (especially aminoglicosides for 6–8 days).

An anti-cholinergic treatment is often associated with CIC: the most used drug is oxybutynin (0.5 mg/kg/die), given directly into the bladder through the catheter, two to three times a day.

20.6.2 Surgical Treatment

It is important to remember that CIC can be performed not only through the urethra, but also through other catheterizable conduits, according to the principle of "continent urinary diversion." The catheterizable conduit is a tubular vascularized structure (e.g., appendix, ureter, ileal tract) which is reimplanted in the bladder, on one side, with an anti-reflux technique, and on the other side it is tunnelled through the abdominal wall and anastomized to the skin in order to obtain a small stoma. Due to this technique, popular in pediatric urology thanks especially to Paul Mitrofanoff, it is possible to perform CIC also when the catheterization by a natural route is difficult or impossible.

20.7 Complications

Complications attributable to CIC are rare and are mostly seen in males [13, 14].

20.7.1 Urinary infection and Asymptomatic Bacteriuria

Although some authors have reported the appearance, during CIC, of febrile urinary infections, it is a common opinion that CIC contributes to reducing the frequency of infections; furthermore, if an episode of infection occurs during treatment, it is very difficult to attribute all the responsibility to catheterism alone.

The presence of an asymptomatic bacteriuria, with a low microbial load, is probably due to the non-sterility of CIC. This bacteriuria, however, when it occurs in patients without vesico-ureteral reflux and who have a complete and periodical vesical emptying, has little importance and does not require any specific treatment. Diokno observed, in 27 patients on CIC for at least 10 years, an incidence of bacteriuria of 74%. There were symptomatic urinary infections only in 2 cases (both with vesico-ureteral reflux) [15].

When a periodic bacteriological evaluation of urine is not possible, the patient's or the family's opinion about the presence of macroscopic anomalies is very important. In the case of turbid and smelly urine, we suggest a rehydrating regimen, associated with endovesical antibiotics for 6–8 days. We consider these episodes acceptable if they occur two to three times a year. If their frequency increases, we suggest a cycle of prophylaxis. If macroscopic anomalies, bacteriuria, or symptomatic infections persist, it is necessary to proceed with a new morphological and functional evaluation of the urinary tract (ultrasound, cystography, urodynamic study, urethral cystoscopy) and to reconsider the technical aspects of CIC together with the patient and his/her family.

20.7.2
Epididymitis

Epididymitis is a well-known complication in the male during CIC, although it is not frequent; however, these episodes seem to be less frequent and easier to treat in patients on CIC than in patients with in-dwelling catheters.

20.7.3
Lithiasis

The follow-up of patients on CIC for a long period rarely shows the appearance of vesical calculi. Also in this case, calculosis is less frequent in patients on CIC than in those with in-dwelling catheters. Renal lithiasis is rare and not referable to CIC. Vesical lithiasis is seen more often in patients on CIC who underwent bladder augmentation or continent diversion. In these cases, however, the role of CIC is only complementary to other important factors, which are the determinants for the genesis of calculi.

20.7.4
Hematuria

Mild and short episodes of hematuria are quite common during CIC. They often resolve spontaneously and do not require a suspension of catheterism. Hematuria is serious more rarely and catheterization becomes difficult and painful: in this case a temporary suspension of CIC and the use of an in-dwelling catheter are advisable. Generally, catheterism can be started again after a few days, preferably after a radiological study of the urethra.

20.7.5
Urethral Stricture

Urethral stricture represents one of the most frequent complications in male patients on CIC; more rarely meatitis, meatal stricture, and false passages. Using prelubricated catheters, reducing the friction on the surface should significantly decrease the percentage of this complication.

20.7.6
Vesical Perforation

Vesical perforation is a rare but very serious complication and causes the bladder to become the origin of an acute abdomen in a patient with a neurogenic bladder. The risk of perforation is higher in patients who underwent an augmentation enterocystoplasty, and in this case the role of CIC is, at best, complementary.

20.8
Conclusion

The urinary complications of a neurogenic bladder consist of the inability to empty the bladder, urinary infection, incontinence, and upper tract deterioration. In 1972 Lapides reported the successful use of clean intermittent catheterization in the management of bladder dysfunction in adults. Rabinovitch in 1974, and Lyon and associates in 1975, reported the successful use of CIC in children with myelomeningocele.

Our experience with CIC in the pediatric age is based on 34 patients, treated since 1995. There were 15 boys and 19 girls. The mean age at starting with CIC was 5 years and 8 months. The cause of the neurogenic bladder was myelomeningocele in 12 patients, caudal regression syndrome in 11, sacrococcygeal teratoma in 2, neurogenic non-neurogenic bladder in 2, and anorectal malformation with sacral anomalies in 7 patients. Children over 5 years of age used self-catheterization, most of them learning the procedure very quickly. Younger children were catheterized by the parents. Our results have been compared with literature data [16–18].

Regarding urinary infection, in our patients we had good results against infection: with the simple use of cranberry juice (without antibiotics) 90% of the patients had sterile urine cultures; 7% had asymptomatic infections; only 3% had symptomatic infections which were treated with antibiotics.

Regarding ureteral reflux, we noted the complete disappearance of reflux in 30% and a significant improvement in 25%. Reflux was unchanged in 45%. No worsening was noted.

Regarding upper tract dilatation, of the pre-existing dilatations 40% improved and 60% were unchanged. We observed no deterioration.

Regarding urinary continence, 56% of the patients were perfectly dry between CIC; 31% had improved but were dry for <3 h; 13% were wet all the time and required complementary treatments (endoscopy or surgery).

Regarding renal function, the blood urea nitrogen and serum creatinine estimations were normal before and during clean intermittent catheterization in all patients.

Regarding complications, no major complications occurred. We had some cases of orchiepididymitis and difficulty in catheterization due to urethritis.

Regarding acceptability of the clean intermittent catheterization program, all our patients found the CIC program acceptable. We never had any problems in convincing parents and patients about the usefulness or necessity of the treatment. None of our patients abandoned the procedure; 2 of them quit CIC because they acquired efficacious micturition, had a bladder "not at risk," and were perfectly continent.

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Pharmacological Therapy in Neuropathic Bladder

21

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21.1
Introduction

The lower urinary tract acts as a group of interrelated structures whose joint function in children brings about efficient low-pressure bladder filling, low-pressure urine storage with perfect continence, and periodic complete voluntary urine expulsion, again at low pressure [144, 145].

This function is regulated by the unique biomechanics of bladder and urethral muscles and coordinated by a complex neural control system located in the brain and spinal cord. The neural control system functioning as a simple switching circuit maintains a reciprocal relationship between the reservoir (urinary bladder) and the outlet components (urethra and urethral sphincter) of the urinary tract. This switching circuit is modulated by various neurotransmitters. Classically, the autonomic nervous system controls bladder function. During the bladder filling (at least in some species) the sympathetic nervous system is activated, increasing the tension of the bladder base and smooth sphincter via activation of alpha-adrenergic receptors and relaxation of the bladder body via activation of beta-adrenergic receptors. The sympathetic activity also inhibits parasympathetic ganglionic transmission via postsynaptic sympathetic fibers, which act upon alpha-2-type receptors located in the ganglion. Meanwhile, the striated sphincter somatic guarding reflex increases outlet resistance to avoid leakage during the filling phase. Emptying involves an inhibition of the spinal somatic and sympathetic reflexes and parasympathetic activation of cholinergic muscarinic receptors of the bladder body, which relaxes the outlet musculature, and this is mediated not only by the cessation of the somatic and sympathetic spinal reflexes but probably also by relaxing factors such as nitric oxide [33, 91, 144, 145].

At the present time, uropharmacology is mostly focused on the autonomic innervation of the bladder and its related structures. In general, the drugs employed for controlling bladder function were originally developed to act on other structures innervated by both cholinergic and adrenergic nerves. These drugs affect lower urinary tract function by initially combining with the special-

Table 1. Factors affecting the capacity of the neuropathic bladder to store and void urine

Storage failure	Voiding failure
Detrusor hyperreflexia	Non-sustained contractions
Detrusor non-compliance	Detrusor–sphincter dyssynergia
Sphincter weakness incontinence	Static sphincteric obstruction
Combinations	Combinations

Table 2. Pharmacological therapy to facilitate bladder filling/urine storage inhibiting detrusor hyperreflexia/increasing bladder capacity

Anticholinergic agents	Increasing outlet resistance
Drugs with mixed actions	Alpha-adrenergic agonists
Drugs acting on membrane channels	Tricyclic antidepressants
Beta-adrenergic agonists	Beta-adrenergic agonists
Tricyclic antidepressants	
Vanilloids	
Botulinum toxin	

Table 3. Pharmacological therapy to facilitate bladder emptying/voiding

Increasing intravesical pressure/bladder contractibility	Decreasing outlet resistance
Parasympathomimetic agents	At the level of the smooth sphincter
Prostaglandins	Alpha-adrenergic antagonist
	At the level of the striated sphincter
	Benzodiazepines
	Baclofen
	Dantrolene
	Botulinum toxin
	Nitric oxide

ized functional components of cells known as receptors. The drug-receptor interaction alters cell function and initiates the series of biochemical, physiological, and urodynamic changes that are responsible for the contraction, relaxation, facilitation, or inhibition, which occur with the use of these drugs. [148]. Many of these drugs affect known mechanisms for neurotransmitter synthesis, transport, storage, release, binding to postjunctional receptors or neurotransmitter inactivation, degradation, or reuptake [148].

This chapter considers different drugs that are available for the treatment of neuropathic bladder dysfunction; however, it must be remembered that, because of their side effects or of the lack of randomized control studies to prove their efficacy and low rate of side effects, only a certain number of these drugs can be used in children.

21.2
Categorization

From a practical point of view the micturition cycle is best divided into two relatively discrete phases that can be summarized as given below [144, 145, 147].

Bladder filling/urine storage requires:

1. Accommodation of increasing volumes of urine at a low intravesical pressure and with an appropriate sensation
2. A bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure
3. Absence of involuntary bladder contractions

Bladder emptying/voiding requires:

1. A coordinated contraction of the bladder smooth musculature of adequate magnitude and duration
2. A concomitant lowering of resistance at the level of the smooth and striated sphincter
3. Absence of anatomic obstruction

This simple overview implies that any type of bladder dysfunction will be the result of an abnormality in one or more of the factors listed above. This two-phase concept of micturition, each phase with the three components that are related either to the bladder or to the outlet, provides a logical framework for the functional categorization of all types of voiding dysfunction and disorders as being related primarily to filling/storage or to emptying/voiding

The classification of a neuropathic bladder dysfunction can also be formulated on a simple functional basis, describing the dysfunction in terms of whether the resulting deficit is primarily one of the filling or the voiding phase of micturition (Table 1).

It is noteworthy that some children do not have an exclusively storage or emptying failure only, and the existence of combination deficits must be recognized to properly utilize this system of classification.

All the known pharmacological drugs for neuropathic bladder dysfunction can be categorized according to whether they are used primarily to facilitate urine storage or emptying, and according to whether their primary effect is on the bladder or on the outlet (Tables 2, 3).

21.3
Therapy to Facilitate Bladder Filling

In children with a neuropathic bladder, the pharmacological treatment of abnormalities related to the filling/storage phase of micturition is directed toward inhibiting bladder contractibility (detrusor hyperreflexia), increasing bladder capacity and/or toward increasing outlet resistance.

21.3.1
Inhibiting Bladder Contractility/Increasing Bladder Capacity

21.3.2
Anticholinergic Agents

Under normal circumstances bladder contraction is predominantly under the control of the parasympathetic nervous system which primarily acts through the muscarinic cholinergic receptor sites on bladder smooth muscle [33]; therefore, atropine and atropine-like agents depress normal bladder contraction of any cause [9, 10]. The M1–M3 receptor subtypes have been identified in the human bladder by receptor binding assays and [154], although M2 receptors are predominant (80% of the total muscarinic receptor population), it is the M3 receptors that mediate bladder contraction [10, 34, 154]. It has also been proposed that co-activation of M2 receptors could enhance the response to M3 stimulation.

Although antimuscarinic agents usually produce significant clinical improvement in patients with involuntary contractions and their associated symptoms, generally only partial inhibition results from their use. In many animal models, atropine only partially antagonizes the response of the whole bladder to pelvic nerve stimulation and of bladder strips to field stimulation. One of the most attractive theories for explaining this phenomenon (“atropine resistance”) is that a major part of the neurotransmission involved in the final common pathway of bladder contraction is secondary to the release of a transmitter other than acetylcholine or norephinephrine [9, 10, 33].

The clinical utility of the available antimuscarinic agents is limited by their lack of selectivity, which is responsible for the classic peripheral anticholinergic side effects: dry mouth; pupillary dilatation; paralysis of accommodation; blurred vision; photophobia; tachycardia; drowsiness; cognitive dysfunction; inhibition of gut motility; and inhibition of sweat gland activity. Agents that possess some ganglionic blocking activity may also cause orthostatic hypotension.

Antimuscarinic agents are generally contraindicated in patients with narrow-angled glaucoma and should be used with caution in patients with bladder outlet obstruction. Although M3 selective agents have the potential to eliminate some of these side effects, it appears that M3 receptors in the lower urinary tract tissues and elsewhere in the body, such as in the glands and brain, are identical [31].

21.3.2.1
Propantheline Bromide

Propantheline bromide is a quaternary ammonium compound that was the first classically described oral antimuscarinic drug for overactive bladder as well as being a nonselective muscarinic antagonist. The antimuscarinic effect of this drug on bladder smooth muscle is similar to the effects of other classic antimuscarinic agents such as glycopyrrolate and isopropamide [139]. Despite its success in uncontrolled case series, no adequate controlled study of these drugs are available and their significant side effects make these older drugs a minimally attractive choice [143, 145].

21.3.2.2
Atropine

This drug is rarely used to treat uninhibited bladder contractions because of its systemic side effects [7]. The pharmacologically active antimuscarinic half of atropine is L-hyoscyamine. This agent (Cystopaz) and hyoscyamine sulfate (Levsin/Levsinex) are reported to have about the same general anticholinergic actions and side effects as the other belladonna alkaloids [143, 145].

21.3.3
Trospium Chloride

Trospium chloride (TCl), an antiparasympathetic quaternary ammonium derivative, has atropine-like effects as well as effects on ganglia and smooth muscle. The drug has a notable antispasmodic activity and hydrophilic properties but does not cross the blood-brain barrier in significant amounts, so any effect on the central nervous system is rare [12]. The compound antagonizes the effect of acetylcholine on cholinergic nerves, and exhibits parasympatholytic action in decreasing detrusor tone and uncontrolled contractions.

It has been widely used in adults with bladder hyperreflexia or instability. Alloussi et al. [4], in a double-blind study with 262 adult detrusor instability patients (178 treated with TCl and 84 with placebo), demonstrated that TCl significantly improved urodynamic parameters such as maximum bladder capacity and volume at first unstable contraction. Cardozo et al. [29], in a similar study with 208 adults treated with TCl, obtained improved urodynamic results very similar to those in the previous study.

In a head-to-head trial of 20 mg of TCl bid vs oxybutynin 5 mg bid, Halaska et al. [71] demonstrated that both drugs were equivalent in so far as decreasing urinary voiding frequency, but TCl had a more favorable dry mouth adverse event profile. In another trial comparing 20 mg TCl bid to 2 mg tolterodine bid, Jünemann and Shukri [82] showed that TCl was statistically more effective in decreasing urinary frequency than the placebo and equivalent to it in decreasing urgency incontinence. Zinner et al. [157], in their study of 523 patients with overactive bladder treated with TCl (20 mg bid), found that this drug significantly decreased the voiding frequency average and mean number urge incontinent episodes as compared with a placebo. It significantly increased the average volume per voiding and decreased average urge severity and daytime frequency. Dry mouth occurred in 21.8% of TCl treated patients and 6.5% of placebo group while constipation occurred in 9.5 and 3.8%, respectively.

Thüroff et al. [140] summarized data from controlled randomized studies on TCl in 1998 and wrote that, on average, 43% of 113 patients reported systemic anticholinergic side effects, although these were recorded as generally mild.

Up to now, there has been very little data published on the efficacy of TCl and its most adequate dosage in pediatric patients.

In a controlled randomized study of 58 children with overactive bladder treated with TCl, Lopez Pereira et al. [93], found that of 50 children treated with TCl, 41 (82%) had a significant positive therapeutic result vs only three who improved in the eight children receiving the placebo (37.5%). In all the responding patients the clinical symptoms either disappeared or decreased markedly, and in 37 (74%) this improvement was accompanied by a urodynamic improvement. In these 37 children, the number of uninhibited contractions decreased by 54.3% and the volume at first contraction increased by 71.4%. There were no statistically significant differences with regard to therapeutic efficacy between TCl dosages (a total daily dosage of 10–25 mg, split into two doses). Only 10% of children experienced adverse effects in this study.

21.3.3.1
Tolterodine

Tolterodine is a new competitive muscarinic receptor antagonist and its efficacy in treating the overactive bladder has been demonstrated in adults [15]. Its selectivity for the bladder is similar to that of oxybutynin, but it is eight times less potent at the antimuscarinic receptor in the parotid gland than the latter [108]. Appell [14] reported on a pooled analysis of a total of 1120 patients in whom tolterodine at doses of 1 or 2 mg twice daily was compared with those of oxybutynin (5 mg three times daily) and of a placebo. Both active drugs significantly decreased the numbers of incontinent episodes and of micturitions in 24 h, and increased the volume voided per micturition in comparison with the effects with placebo. There were no differences in efficacy between these drugs but tolerance was significantly better with tolterodine (less adverse events such as dry mouth). Similar findings with respect to equal efficacy and better tolerability with tolterodine than oxybutynin have been reported by other authors [2, 50].

Unfortunately, very few studies have examined the effects of this drug in children. In a study of 22 children with detrusor hyperreflexia, Goessl and colleagues [64] used tolterodine either as a replacement therapy for oxybutynin or as initial treatment. All patients received a total of 0.1 mg/kg oral tolterodine tartrate daily, divided into two doses. Tolterodine was found to be equal to oxybutynin in efficacy and had fewer adverse effects in the group that had previously been treated with oxybutynin. In a study of 33 children with overactive bladders different dosages (0.5, 1, 2, and 3 mg twice daily) of oral tolterodine demonstrated linear pharmacokinetics and excellent efficacy in decreasing voiding frequency and incontinence episodes [77]. Bolduc et al. [23] reviewed 34 children with dysfunctional voiding (urgency, frequency, and daytime wetting) who were prospectively crossed-over from oxybutynin to tolterodine (1–2 mg twice daily) because of oxybutinin side effects. Twenty patients (59%) reported no new side effects, 6 described the same but more tolerable side effects as with oxybutynin, and 8 patients discontinued tolterodine because or its side effects. The efficacy of tolterodine was comparable to that of oxybutynin. The reduction in wetting episodes was >90% in 23 patients, more than half in 5 and less than half in 6 patients.

A new form of extended-release tolterodine (Tolterodine LA) has recently been introduced. It should have equal efficacy and fewer side effects. A study [141] compared the efficacy and safety of tolterodine LA, immediate-release tolterodine, and placebo in 1529 adults with overactive bladder and found a statistically better efficacy for decreasing urge incontinence with tolterodine LA vs immediate-release tolterodine (71 vs 60%) as well as a lower incidence of dry mouth (23 vs 31%).

21.3.3.2
Darifenacin, Vamicamide, Solifenacin Succinate

These agents are selective for M3 receptors, which [105,151] are also present in the salivary glands as well as the bladder; therefore, it is important that the new drugs be tissue selective rather than receptor selective in order to minimize the side effects. Solifenacin succinate, a bladder selective antimuscarinic agent, which is currently being investigated in cases of detrusor overactivity for response and side effects, has shown promising results. Chapple and colleagues [35], in a multicenter-controlled study, compared different doses of solifenacin (2.5, 5, and 10, 20 mg) with tolterodine (2 mg twice daily) and placebo, in 265 patients with overactive bladder. There was a significant increase in voided volume and a reduction in voiding frequency in three of the solifenacin dose groups (5, 10, and 20 mg) as compared with effects with the placebo. The improvement in these parameters was also greater in the solifenacin groups than in the tolterodine group, but this study design did not adequately compare these two agents. The incidence of dry mouth was lower for solifenacin (5 and 10 mg) than for tolterodine (14 vs 24%).

More studies are ongoing to determine the efficacy and tolerability of these drugs and all of them are still under investigation.

21.3.4
Drugs with Mixed Action

21.3.4.1
Oxybutynin Chloride

Oxibutynin chloride is a well-known antimuscarinic agent with some affinity for M3 and M1 receptors and with a pronounced muscle relaxant activity as well as anaesthetic activity [34,138]. Its efficacy for lowering detrusor pressure and in abolishing unwarranted contractions has been documented in neonates and children [18, 75, 84, 103, 115]. In a study of 41 children with myelomeningocele and detrusor hyperreflexia who were evaluated before and within months after the initiation of therapy, oxybutynin chloride (0.2–0.3 mg/kg day^{-1}) significantly increased the maximal bladder capacity and decreased the detrusor pressure at maximal capacity. Continence was also improved in 70% of patients who were incontinent before therapy [63].

The major problem with oxybutynin is its high rate of side effects. Dry mouth, constipation, and heat intolerance are seen in almost a third of patients and are some of the main reasons for dropout [80, 107]. The drug can cross the blood-brain barrier and psychological and personality changes may be seen. Anecdotal documentation of improvement in school achievements following withdrawal of the drug in myelomeningocele patients support this possible side effect [106].

To overcome this problem a slow-release form of the drug has been developed. Studies in adults and children have demonstrated the same success rate with better tolerability with the slow-release formulation than with the classic formulation [7,155].

It has been suggested that most extended-release oxybutynin absorption occurs in the large intestine rather than in the stomach and proximal intestine. This different site of drug absorption (which can also occur with intravesical administration) limits the formation of oxybutynin metabolites (N-desethyl-oxybutynin). Oxybutynin metabolites and not oxybutynin chloride itself may be responsible for most of the side effects, including dry mouth [37, 48, 67, 68].

Another alternative for reducing oxybutynin side effects is intravesical administration. In different studies intravesical instillation of oxybutynin has been proven to be successful in lowering detrusor pressure with fewer side effects compared with immediate release oral administration [65, 99, 111]. Many different preparations have been described for use in children. One very common method consists of the dissolution of a 5-mg tablet of oxybutynin chloride in 30 ml sterile saline solution which is then instilled into the bladder via catheter. The daily dosage and frequency remain undefined, but most authors recommend using the medication three times a day. In a study that compared the side effects, Ferrara et al. [56] demonstrated that intravesical administration was safer and better tolerated than oral oxybutynin; however, of 34 children, six still had undesired side effects including drowsiness, hallucinations and cognitive changes. Amark et al. [5], in a study of 39 children with neuropathic bladder and detrusor hyperreflexia treated with intravesical oxybutynin (0.1 mg/kg twice daily), reported only two side effects; however, adverse effects such as cognitive impairment can also occur in children treated with intravesical oxybutynin [94, 96].

Transcutaneous application of oxybutynin can also decrease side effects, while still maintaining efficacy and increasing patient compliance. Davila et al. [41] recently reported the outcome of a multicenter randomized double-blind study of transdermal vs immediate-release oral oxybutynin. Transdermal oxybutynin achieved a similar decrease in urge incontinence episodes but produced significantly fewer episodes of dry mouth than oral administration.

Another administration route that could possibly reduce side effects and improve patient compliance is the use of rectal suppositories [150]; however, so far there is no experience with these two new forms of therapy in children and, even in adults, more studies are necessary to confirm its efficacy and tolerability.

21.3.4.2
Propiverine

Propiverine has a pharmacological profile that is similar to that of oxybutynin, with direct antimuscarinic myotropic relaxant properties, and it also has local anesthetic activity. Stöhrer et al. [135] reported a double-blind randomized trial comparing propiverine, 15 mg three times a day, to placebo in 113 spinal cord injury patients with detrusor hyperreflexia. Changes in maximum bladder capacity at first contraction and in maximum bladder contraction were statistically significant. Bladder compliance showed a more pronounced increase with propiverine treatment than with the placebo. Of the patients, 37% experienced dryness of the mouth and 28% had accommodation disorders compared with the 8 and 4%, respectively, in patients receiving a placebo. Madersbacher et al. [95] compared propiverine with oxybutynin in patients with urgency and urge incontinence. Urodynamic efficacy was judged to be similar to that of oxybutynin, but the incidence of dry mouth was lower. Marschall-Kehrel et al. [98], in a retrospective study of 70 children with urge syndrome and urge incontinence treated with propiverine (0.4 mg/kg, two times daily), report 29 children achieving continence and an improvement in functional bladder capacity to values that were at least normal for their age. Only one adverse event was reported in 1 child (accommodation disorder). Batinic et al. [19], in a randomized, double-blind, placebo-controlled clinical trial of 266 incontinent children with concomitant urge symptoms, showed propiverine and oxybutynin to be equally effective, and there were no differences in the incidence of side effects between propiverine and the placebo. Nevertheless, its use for neuropathic bladder dysfunction has been quite limited given the lack of sufficient studies to evaluate the effectiveness and tolerability of propiverine in paediatric patients.

21.3.4.3
Dicyclomine Hydrochloride

In addition to its antimuscarinic action, dicyclomine hydrochloride is reported to possess a direct relaxant effect on smooth muscle. An oral dose of 20 mg three times a day in adults reportedly increased bladder capacity in patients with detrusor hyperreflexia [58]. Beck et al. [21] compared the effects of 10 mg of dicyclomine, 15 mg of propantheline, or a placebo three times a day in patients with detrusor hyperreflexia. The reported cure or improvement rates were 62, 73, and 20%, respectively; however, the reported efficacy of this drug is based only on clinical studies without controls, since, as yet, there have been no good-quality randomized control trials in adults, and there is still no experience with the use of this drug in children.

21.3.5
Drugs Acting on Membrane Channels

21.3.5.1
Calcium Antagonists

The role of calcium as a messenger in linking extracellular stimuli to the intracellular environment is well established, including its involvement in excitation–contraction coupling in striated, cardiac, and smooth muscle [33]; therefore, interfering with calcium inflow or intracellular release is a very potential mechanism for bladder smooth muscle relaxation, and many experimental studies have confirmed the inhibitory effect of calcium antagonists in a variety of experimental models of spontaneous and induced bladder muscle strip activity [11,149].

However, the available information does not suggest that oral therapy with calcium antagonists, such as terodiline, among others, is currently an effective way to treat detrusor hyperrreflexia [144145].

21.3.5.2
Potassium Channel Openers

Potassium channel openers efficiently relax various types of smooth muscle, including detrusor smooth muscle, by increasing potassium efflux and producing membrane hyperpolarization. This hyperpolarization reduces the opening probability of ion channels (primarily calcium) involved in membrane depolarization and, by that, can produce relaxation or inhibition of contraction [11,144].

Theoretically these drugs could abolish bladder hyperactivity without affecting normal bladder contraction. Pinacidil and cromakalin are the first-generation ATP-sensitive potassium channels openers but, to date, there is no clinical evidence to support the use of these drugs to treat detrusor hyperreflexia in children or adults [145].

21.3.6
Beta-Adrenergic Agonists

The sympathetic nervous system induces bladder body relaxation via a population of beta-adrenergic receptors; thus, drugs with beta-adrenoceptor agonist activity inhibit nerve-induced contractions of detrusor muscle in vitro, so the administration of these drugs in children could increase bladder capacity [144145]. The results of different studies with beta-adrenoceptor agonists, such as terbutaline and clenbuterol, have been inconsistent and might be explained by the recent discovery of a beta-3-adrenoceptor agonist in human detrusor muscle [81,137]. The future development of beta-3-adrenoceptor agonists will probably increase the clinical efficacy.

21.3.7
Tricyclic Antidepressants

Different authors have suggested that tricyclic antidepressants, particularly imipramine (tofranil), are useful agents for facilitating urine storage and could act in two ways: (a) decrease bladder contractibility; and (b) increase outlet resistance [142,143].

Clinically, imipramine has been reported to be effective in decreasing bladder contractibility and increasing outlet resistance [30, 116].

It has been known for many years that imipramine is relatively effective in the treatment of childhood nocturnal enuresis. The usual recommended dose is 0.7–1.2 mg/kg, two to three times daily.

The exact mechanism by which imipramine inhibits bladder activity is unknown, but it has been postulated that this effect may be caused by an increase in serotonin concentration (from reuptake blockade) in the lower spinal cord. This may involve a direct inhibition of normal excitatory pathways or a depression of afferent ascending neural activity [11, 55]. Nevertheless, its use in patients with neuropathic bladder dysfunction has been quite limited and there have not been enough studies to evaluate its effectiveness and tolerance in children.

Side effects are usually infrequent but personality changes, adverse effects on sleep and appetite, gastrointestinal symptoms, and nervousness have been reported in children [83, 129]. The use of this drug is contraindicated in patients receiving monoamine oxidase inhibitors, because severe CNS toxicity can be precipitated and induce hyperpyrexia, seizures, and coma.

21.4
Decreasing Sensory (Afferent) Input: Vanilloids

21.4.1
Capsaicin

Capsaicin is the main pungent ingredient in the "hot" pepper genus *Capsicum*. It is a specific neurotoxin that desensitizes C-fiber afferent neurons, which may be responsible for the signals that trigger detrusor overactivity. Studies with intravesical instillation of capsaicin have demonstrated its clinical efficacy, but most have also shown that acute pain and irritation associated with capsaicin are a major deterrent to widespread use [144].

21.4.1.1
Resiniferatoxin

Resiniferatoxin is a much more potent sensory antagonist than capsaicin. It has vanilloid receptor agonist activity and can produce desensization; however, since it acts without the potent neuronal excitatory effect of capsaicin, it produces less discomfort. Consequently, it has the potential to act as an alternative to capsaicin that would be potentially therapeutic for overactive bladder induced by hyperexcitability of C-fiber bladder afferents.

In neuropathic bladders an intravesical application of resiniferatoxin at high doses (50 and 100 nM) has been shown to decrease the frequency of micturition for up to 3 months [39]. Furthermore, the same dosage produced an improvement in symptoms that lasted longer, up to 12 months in 7 of 14 patients [130].

There is a single case reported in the literature on the use of this drug in a child. A 9-year-old boy with low bladder compliance and bilateral grade-II vesicoureteral reflux, failed to respond adequately to either oral and intravesical oxybutynin or CIC. A resiniferatoxin saline solution (50 ml at a concentration of 10^{-6} M) was tried intravesically. Three months later, the boy showed no vesicoureteral reflux and his bladder compliance had improved [128].

Although this drug has potential for use in children with a neuropathic bladder, many more studies are needed to determine its efficacy and safety in this population.

21.4.1.2
Botulinum Toxin

Botulinum toxin (BTX), the most potent biological toxin known, is synthesized by *Clostridium botulinum*, an obligate anaerobic bacterium. Since the 1980s BTX has been used to treat various conditions in which muscle inactivation may be useful, including strabismus, dystonia, and spasticity.

Blockage of acetylcholine release at the neuromuscular junction is the most obvious sign of BTX poisoning and readily causes a flaccid muscular paralysis [25]. Nevertheless, exocytosis of other neurotransmitters, including noradrenaline, dopamine, serotonin, gamma-aminobutyric acid, and glycine, is also inhibited by BTX. In addition, the toxin may also compromise the release of glutamate and substance P from peripheral sensory fibers [13, 73, 132].

Histological observations show that the intoxicated nerve terminals degenerate while buds, which have the ability to form functional synapses, soon begin to sprout in other parts of the affected nerves producing a progressive return of the synaptic activity to the original nerve terminals. Unnecessary buds are gradually eliminated and full recovery from chemodenervation occurs within 3–6 months [13, 89].

BTX-A has been the most frequently used serotype to treat urological conditions. Different studies in adults with neuropathic bladder using BTX-A (intravesical injections) have demonstrated a significant increase in bladder capacity, with a significant decrease in maximum detrusor pressure and an improvement in continence [43, 117, 118, 125].

BTX-A has also been assayed in children with myelomeningocele and detrusor hyperreflexia [3, 38, 120, 123]. Overall, 71 children with urinary incontinence that was refractory to anticholinergic therapy and CIC were recruited. The dose varied between 4 and 12 units/kg weight, the total amount not exceeding 300 units. As in adults, the toxin increased bladder capacity and decreased maximum detrusor pressure. Full continence ranged between 68 and 86% [38, 120]. The duration of detrusor paralysis after each treatment was apparently identical to that observed in adults. [120, 123].

In a prospective study BTX-A was injected under anesthesia at 30–40 sites (85–300 U) into the bladder wall of 17 children; all had recorded intravesical pressures greater than 40 cm of water despite a high dosage of anticholinergic medication. A urodynamic study performed 2–4 weeks after the injection showed a significant increase in bladder capacity and detrusor compliance; however, there was a decrease in incontinence episodes, but this difference was not significant. No side effects were noted, except one child who had increased post-voiding residual urine [122].

To date, there are no long-term results on the efficacy and safety of BTX-A in children, and moreover, in other settings, the effects of this treatment lasted only a few months, so that repeat treatments are necessary. Although promising, more studies are needed to validate these results.

21.5
Increasing Outlet Resistance

21.5.1
Alpha-Adrenergic Agonists

There is a high concentration of alpha-receptor sites in the trigone, bladder neck and proximal urethra, and, when stimulated, they produce smooth muscle contraction.

Alpha adrenergic agents increase maximum urethral pressure and maximum urethral closure pressure and this alters the static infusion urethral pressure profile. Generally, these drugs increase outlet resistance to variable degrees [33, 144, 145].

The side effects included blood pressure elevation, anxiety, insomnia, headache, tremor, weakness, palpitations, cardiac arrhythmias, and respiratory difficulties.

The alpha-1A-adrenergic receptor subtype is predominant in the human lower urinary tract, but another alpha-1L subtype has been proposed as mediating phenylephrine-induced contractions in the human urethra, and this possibility offers an opportunity for increased uroselectivity[109].

Ephedrine is a noncatecholamine sympathomimetic agent that enhances norephinephrine release from sympathetic nerves while directly stimulating both alpha- and beta-adrenergic receptors. The ephedrine stereoisomer, pseudoephedrine, has similar indications and requires the same precautions as ephedrine.

Phenylpropanolamine shares the pharmacological properties of ephedrine and is approximately equal in peripheral potency, but it has a less intense effect on the CNS. This agent is a component of numerous proprietary mixtures, some marketed for the treatment of nasal and sinus congestion, and some marketed as appetite suppressants. [144, 145].

21.5.1.1
Tricyclic Antidepressants

The actions of tricyclic antidepressants has been discussed in the section on inhibiting bladder contractility. Theoretically an increase in urethral resistance might be expected if an inhibition of norephinephrine reuptake had enhanced the alpha-adrenergic activity in the bladder [144145].

21.5.2
Beta-Adrenergic Agonists

Beta-adrenergic stimulation is generally thought to decrease urethral pressure, although beta-2 agonists have been reported to increase the contractility of fast-contracting striated muscle fibers [9]. Clenbuterol, a selective beta-2 agonist, has been reported to potentiate the field stimulation-induced contraction in isolated periurethral muscle preparations in the rabbit in a dose-dependent fashion [86].

Nevertheless, all of these drugs – the alpha-adrenergic agonists [17, 20, 46, 54, 133], beta-adrenergic agonists [62,153], and tricyclic antidepressants [61, 92] – have been used to increase outlet resistance in adults with different successful results, and only in certain selected cases of mild stress incontinence can they produce a beneficial effect. On the other hand, no adequately designed controlled studies of any of these drugs for treating neuropathic sphincteric deficiency have been published, and therefore, as of the time of writing, no proven treatment is available that will enhance bladder outlet resistance in children with neuropathic sphincter deficiency.

21.6
Therapy to Facilitate Bladder Emptying

Treatment for emptying failure generally consists in attempts to increase intravesical pressure, decrease outlet resistance, or both.

Thirty-two years of worldwide experience has made clean intermittent catheterisation (CIC) the primary choice for bladder emptying in the treatment of children with neuropathic bladder dysfunction. In those cases in which the detrusor does not show any activity (arreflexia) and there is static sphincter obstruction, or when a detrusor–sphincter dyssynergia exists, CIC is still the best method to empty the bladder at regular intervals while maintaining low intravesical pressure, with maximum efficacy and minimal side effects; thus, the use of drugs to facilitate bladder emptying is not recommendable in children with neuropathic bladder dysfunction and high post-voiding residual urine. On the other hand, neurourologists have still not found the ideal pharmacological treatment for urodynamically significant detrusor–sphincter dyssynergia.

21.7
Increasing Intravesical Pressure

21.7.1
Parasympathomimetic Agents

Generally, the final common pathway in physiological bladder contraction is stimulation of parasympathetic postganglionic muscarinic cholinergic receptor sites, and thus, agents that imitate the actions of acetylcholine might be expected to be effective in treating patients who cannot empty because of inadequate bladder contractility. Many acetylcholine-like drugs exist, but only bethanechol chloride (Urecholine) exhibits in vitro relatively selective actions on the urinary bladder and gut with little or no nicotinic action [26]. Bethanechol is cholinesterase resistant and causes in vitro contractions of smooth muscle from all areas of the bladder [156]; however, despite the potential side effects of these drugs (flushing, nausea, vomiting, diarrhea, gastrointestinal cramp, etc), all of these drugs have been documented to have beneficial effects [8, 57].

21.7.2
Prostaglandins

The reported use of prostaglandins to facilitate emptying is based on the hypothesis that these substances contribute to the maintenance of bladder tone and bladder contractile activity [11]. Stimulation of detrusor activity by intravesical instillation of prostaglandins has been reported to be successful [27]; however, the effect is controversial and no placebo-controlled studies are available to validate the efficacy and safety of these drugs [66].

21.8
Decreasing Outlet Resistance

21.8.1
At the level of the smooth sphincter

21.8.1.1
Alpha-Adrenergic Antagonists

Although the human lower urinary tract contains more alpha-2 than alpha-1 adrenergic receptors, prostatic smooth-muscle contractions are provoked predominantly, if not exclusively, via alpha-1 receptors [36, 76, 90, 102]. At least three subtypes of alpha-1 adrenergic receptors exist: alpha-1A; alpha-1B; and alpha-1D [101]. Different studies have shown that smooth muscle contraction in the human lower urinary tract is mediated largely by the alpha-1A subtype [47, 72]. In addition to the three known alpha-1 receptors, there is a possible fourth receptor (alpha-1L) that is probably a variant of alpha-1A. Stimulation of the alpha receptors will contract smooth muscle and increase outlet resistance; thus, an alpha-adrenergic blockade would theoretically result in smooth muscle relaxation at the base of the bladder and decrease outlet resistance in the proximal sphincter complex.

Krane and Olsson in 1973 [87] were among the first to demonstrate that treating neuropathic patients with nonselective alpha-blocker, phenoxybenzamine, may significantly improve emptying. They and many others have confirmed the effectiveness of treating voiding dysfunction with alpha receptor-blocking agents in adults with a neuropathic bladder [1, 126, 136, 146, 152].

Some authors assumed that alpha-blocking agents not only decreased the smooth muscle activity of the bladder outlet but also acted on alpha-receptors in the detrusor wall, and directly decreased detrusor hyperactivity [110].

Swierzewski et al. found improved detrusor compliance in patients with spinal cord injury after treatment with terazoxin. An explanation for this might be in the article by Restorick and Mundy in 1989 [119]: they found almost four times as many alpha-adrenoreceptors in the detrusor tissue of patients with bladder overactivity than in tissue from people with normal bladder activity.

This additional effect at the bladder level could provide a further benefit for neuropathic pediatric patients in whom there is bladder body and outlet pathology. In addition, although controversial, some authors have suggested that these agents may also decrease striated sphincteric tone [40, 59]. One explanation for this could be that alpha blockers that cross the blood-brain barrier might contribute to decreased urethral resistance through two mechanisms; the well-known blockade of peripheral receptors in the bladder outlet and the reductions in central pre-ganglionic sympathetic (hypogastric) neuronal activity and in somatic activity via pudendal motor neurones that innervate the external sphincter

Although alpha blockers have been widely used in children to treat hypertension, their role in the management of bladder outlet obstruction remains relatively unexplored.

In 1975, Stockamp [134] reported using nonselective phenoxybenzamine in five children with upper tract complications due to functional infravesical obstruction. After initiating alpha-blocker therapy all patients had decreased outlet resistance, detrusor pressure and post-voiding residual urine. In addition, hydronephrosis decreased in all and was completely resolved in three. Another five reports involve a similar use of these nonselective alpha blockers (phentolamine, phenoxybenzamine) in children with neuropathic bladders and most of these studies noted an improvement in bladder emptying with decreased post voiding residual urine [6, 42, 74, 100, 127], urethral profile pressure, and detrusor pressure; however, further use of these early nonselective alpha-adrenergic antagonists (alpha-1 and alpha-2 blockers) did not flourish, presumably due to concerns about their significant side effects (postural hypotension, dizziness, and asthenia).

The preponderance of the alpha-1 adrenergic receptors at the bladder outlet and along the urethra made it possible to use a selective alpha-1 adrenergic antagonist to decrease the outlet resistance in some children with neuropathic bladder. Some of the most common selective alpha-1 antagonists are prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin. These alpha-1 antagonists are being investigated for the treatment of overactive pelvic floor muscles and sphincter muscles. In a small trial (n=17), doxazosin, starting at 0.5–1 mg nightly, improved bladder symptoms in 82% of children with inadequate bladder emptying of various etiologies including non-neuropathic and neuropathic dysfunctional voiding. Post-voiding residual urine decreased in about 71% of responders. Only 1 patient had a mild postural hypotension and this was resolved by reducing the dose [16]. Schulte-Baukloh et al. [121] assessed the efficacy of alfuzosin (2.2–7.5 mg/day) to decrease detrusor leak point pressure in 17 children (mean age 6.3 years) with neuropathic bladder. The mean detrusor leak-point pressure decreased from 68 to 46 cm of water (p<0.01), the reflex volume (defined as the volume at the first uninhibited contraction >15 cm of water) increased from 78 to 112 ml (+44%), and bladder compliance increased from 9.3 to 19.6 ml/cmH_2O (+111%). Maximal vesical pressure decreased from 84 to 70/cmH_2O (-17%) and the mean number of uninhibited contractions decreased from 6.3 to 3.5 (-44%). Intermittent catheterization could be avoided in six children; however, in this study 9 patients had a concomitant therapy (CIC and/or anticholinergics) and alfuzosin was successful in only 50% of the patients (in whom the decrease in leak point pressure had therapeutic consequences). Two mothers complained about their children's sleepiness and one child had mild dizziness.

Cain et al. [28] evaluated the outcome of alpha blocking therapy (doxazosin) in 55 children (mean age 7.9 years) with urinary incontinence, urgency, urinary tract infection, and poor emptying with residual urine. The initial dose was 0.5 mg daily, which was increased incrementally to a maximum of 2 mg daily until improved bladder emptying was documented. All patients were also treated with behavioral modification and 47 patients with anticholinergic medication. After starting doxazosin, the average post-voiding residual urine decreased to 8 ml (88% reduction in residual urine). Side effects occurred in 2 patients who stopped the medication (heart murmur, dizziness).

A limitation of this study and the previous study is that patients had been treated with other therapies that may also have improved bladder emptying. Moreover, the addition of anticholinergics could also potentially have decreased outlet resistance, thereby improving emptying.

Recently, Donohoe et al. [49], reported 26 children (mean age 12.8 years) with primary bladder neck dysfunction treated with terazosin, doxazosin, or tamsulosin. Mean average and maximum uroflow rates improved from 5.5 to 12.6 cc/s and from 10.3 to 19.7 cc/s, respectively. The mean EMG lag time decreased from 24.4 to 5.7 s and post-voiding residual urine volume from 98.9 to 8.9 ml (all p<0.001). Of the eight patients with incontinence, seven became continent (five of these were also treated with oxybutynin). Nineteen children were eventually switched to tamsulosin (average dose of 0.4 mg; range 0.2–0.8 mg)) and one-third of the patients receiving tamsulosin reported mild degrees of headache, somnolence, nasal congestion, and nausea, while mild to moderate degrees of at least one of these side effects and/or dizziness were reported by three-quarters of those treated with terazosin or doxazosin.

Despite some studies supporting the suggestion that alpha-adrenergic blockade may be effective in neuropathic and non-neuropathic bladders with a functional outlet obstruction, the number of these studies is very limited and none are a randomized studies; therefore, further investigations, including prospective randomized trials of alpha-blocker therapy in children with neuropathic and non-neuropathic urinary tract dysfunction, as well as long-term follow-up studies, are needed to validate the potential role of selective alpha-blocker therapy for children.

21.8.2
At the Level of the Striated Sphincter

21.8.2.1
Benzodiazepines

Gamma-aminobutyric acid (GABA) and glycine have been identified as major inhibiting transmitters in the CNS. Benzodiazepines potentiate GABA action by facilitating neuronal hyperpolarization through the $GABA_A$ receptor. Side effects include non-specific CNS depression (sedation, lethargy, drowsiness, ataxia, and decreased ability to acquire or store information). There is a real absence of data to demonstrate an advantage of these agents over a placebo effect in the treatment of detrusor–sphincter dyssynergia secondary to neurological disease, while, at the same time, the known side effects of these drugs minimize their overall usefulness [144145].

21.8.2.2
Baclofen

Baclofen depresses mono- and polysynaptic excitation of motoneurons and interneurons in the spinal cord by activating GABA $_B$ receptors. In 1977, Hachen and Krucker [69] found that a daily dose of 75 mg orally was ineffective in patients with striated sphincter dyssynergia, but that a daily IV dose of 20 mg was highly effective; however, the hydrophilic properties of GABA prevent it from crossing the blood-brain barrier in sufficient amounts to made it therapeutically useful. For oral use, the more lipophilic analogue baclofen was developed. Nevertheless, the passage of this drug through the barrier is also limited and it consequently generally insufficient when given orally to treat micturition disorders secondary to neuropathic dysfunction [44].

21.8.2.3
Dantrolene

Dantrolene exerts its effect by a direct peripheral action on skeletal muscle. It inhibits the excitation-induced release of calcium ions from the sarcoplasmic reticulum of striated muscle fibers [32]. This drug has been reported to improve function in some patients with detrusor–sphincter dyssynergia [104]. Hackler et al. [70] reported improvements in voiding function in 50% of their patients treated with a minimum daily oral dose of 600 mg dantrolene. The generalized weakness that this drug produces can compromise its therapeutic effects and it can also induce euphoria, dizziness, diarrhea, as well as hepatotoxicity.

21.8.2.4
Nitric Oxide

Nitric oxide (NO) is synthesised by a family of enzymes known as nitric oxide synthases (NOS) that catalyse the conversion of the amino acid L-arginine to NO. NOS-staining neurones have been identified in very high density in the urethral of cats, guinea pigs, and humans [60, 78, 79, 85, 114, 131]. Nitric oxide is thought to play an important regulatory role in striated urethral sphincter relaxation, probably mediated via cyclic GMP through the activation of cyclic GMP-dependent protein-1 kinase [112]. In vivo, NOS inhibitors reversibly reduce or abolish the magnitude and duration of urethral relaxation during micturition in both rats and pigs as well as in humans [22, 24, 53]. The NO donors, such as glyceryl trinitrate or isosorbide mononitrate, could be used to deliver NO to the external sphincter. The external sphincter has a rich blood supply and thus NO, administered sublingually or orally, should reach the urethral sphincter in high concentrations.

Mamas et al. [97] recently hypothesized that NO donors could be a potential new treatment option for detrusor striated sphincter dyssynergia.

Reitz et al. [117], in an acute study, treated 12 men with spinal cord injury and detrusor–sphincter dyssynergia with 10 mg of sublingual isosorbide dinitrate. The cystommetry study 15 min after drug administration revealed a reduction in external urethral sphincter pressures at rest and during dyssynergic contraction. Seven of the 12 patients complained of headache after drug administration. This promising early report may motivate new studies to evaluate the efficacy and safety of chronic administration of this drug in the treatment of detrusor-striated sphincter dyssynergia.

21.8.2.5
Botulinum Toxin

As discussed previously, this agent inhibits acetylcholine release at the neuromuscular junction between somatic nerves and striated muscle. Its urological use for the treatment of detrusor-striated sphincter dyssynergia was first reported by Dykstra and Sidi [51] and Dykstra et al. [52]. In both studies, as well as in other small studies [113, 124], a BTX-A injection in the urethral sphincter decreased urethral pressure, bladder pressure during voiding, as well as post-voiding residual urine for 2–3 months. In a more recent study, Kuo [88] reported a urethral sphincter injection in 29 patients with detrusor–sphincter dyssynergia. A total of 50–100 UI were applied under cystoscopy at the 3, 6, 9, and 12 o'clock positions. Voiding pressure and post-voiding residual urine decreased by at least 25% decrease in 28% of the patients. Smaller improvements were also found in another 52% of cases. The responders maintained the effect for at least 4 months. A small randomized study compared 100 UI BTX-A (n=5) with 0.5% lidocaine (n=8) diluted in a total volume of 4 ml and injected in the urethral sphincter by transperineal needle. Only patients treated with BTX-A showed a significant decrease in post-voiding residual urine volume and maximum detrusor pressure [45].

A potential side effect after BTX-A injection was a mild muscular weakness in the upper extremities that could persist for 2–4 weeks, and this side effect was more probable when high volumes of BTX-A were injected [43]. Although these results in adults are promising, there are still not enough studies in adults or children to validate the efficacy and tolerability of BTX-A treatment for neuropathic detrusor-striated sphincteric dyssenergia of neuropathic origin.

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Pelvic Floor Therapy

22

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22.1
Introduction

Dysfunctional voiding is one of the major causes of daytime wetting in children, as well as one of the causes of vesicoureteral reflux and recurrent urinary tract infections. This population comprises approximately 40% of all patients seen by pediatric urologists [5]. While some quote prevalence rates of 5–6%, others have found dysfunctional voiding rates to be as high as 65% of children between 5 and 9 years of age with urinary tract infections and 23% of those without [6]. It is found more commonly in females than males by a 4:1 ratio.

Besides the risk of medical problems, such as recurrent lower urinary tract infections and pyelonephritis, dysfunctional voiding leading to incontinence can be a difficult psychosocial problem. Children have been shown to rate wetting themselves at school as the third most catastrophic event that could ever occur, behind the death of a parent and going blind [24]. Daytime wetting obviously causes significant psychological morbidity, and for that reason alone, definitive treatment is of the utmost importance.

Pelvic floor therapy plays a major role in the treatment of dysfunctional voiders, including those that have resulting detrusor external sphincter dyssynergia (DSD). DSD is characterized by involuntary contractions of the striated musculature of the urethral sphincter during a voluntary or involuntary detrusor contraction. It is also seen in patients with neurologic lesions between the brain stem and the sacral spinal cord; however, it has been found that pelvic floor therapy does not improve DSD in children with known neurologic lesions such as spina bifida or sacral agenesis [8]. Its primary role is in treating the neurologically normal group of children with dysfunctional voiding.

Dysfunctional voiding can be defined as any functional abnormality that results in abnormal voiding. In this chapter, the term “dysfunctional voiding” is used to describe the noncoordination between the bladder and the external sphincter. This is in contrast to the term “voiding dysfunction,” which is a global expression encompassing not only dysfunctional voiding but also other urinary conditions such as nocturnal enuresis. The most common cause of dysfunctional voiding is contraction of the pelvic floor muscles during voiding in the absence of anatomic obstruction [23]. Dysfunctional voiders can vary widely in terms of manifestation, prognosis, response to treatment, and pathophysiology. Other terms commonly used to describe the bladder of a dysfunctional voider is nonneurologic neurogenic bladder, Hinman’s syndrome [14], “lazy” bladder, or occult neuropathic bladder, all of which refer to neurologically normal children [34].

Dysfunctional voiding can be treated in a variety of ways, ranging from medical to surgical interventions for severe cases. Treatment of dysfunctional voiding in nonneurologic neurogenic bladders should begin with behavior modification using a timed voiding program. If there is evidence of hyperactive urethral sphincter activity, pelvic floor therapy will not only help resolve symptoms but will also potentially cure the underlying problem.

22.2
History

Dr. Arnold Kegel in 1948 noted that female pelvic muscles after childbirth “…having been stretched over a wider range than any other muscle (the pelvic floor muscles) can regain physiological tension and are able to recover their function after many years of disuse and partial atrophy." He began teaching his patients to forcefully and intentionally contract their pelvic muscles, known as pelvic floor exercises or "Kegels," to treat and prevent postpartum incontinence. He routinely employed a perineometer with his patients, which is one of the first documented uses of biofeedback in medicine [17].

One step beyond simple Kegel exercises is the use of vaginal cones for female incontinence. The cones are inserted into the vagina and the patient practices tightening the pelvic muscles in order to keep the cones from slipping. When the patient can easily hold the lightest cone, a succession of heavier cones is then used. This gives the patient biofeedback about improvement in strength as well as technique. While this type of biofeedback can have a satisfaction rate of 40–70%, there is the Tissue of compliance, which is the largest hurdle in any type of biofeedback program [26].

In treatment of urinary incontinence in adults, the goal is learning how to contract the pelvic floor muscles in order to help achieve continence. In children, it is usually the opposite, with the main goal of biofeedback being pelvic floor relaxation. In general, however, the principles of pelvic floor therapy remain the same in any population and with any end point. Biofeedback is any method of training that teaches a patient to control a bodily function by providing him or her with information about that function. This information can be relayed to the patient verbally, after digital feedback, after examination, through the sensation of vaginal cones, or with mechanized equipment emitting audio or visual signals that correlate to the function [34].

Beer and Allen were the early pioneers in the assessment and treatment of pediatric dysfunctional voiding in the 1960 and 1970s [2]. They identified the discoordination between the pelvic floor and the bladder as a clinical entity, which they felt was a learned behavior brought on by potty training [23]. Then in the early 1980s, urodynamic evaluation was extended into the pediatric population and investigators such as Bauer, focused on treatment based on urodynamic findings. The emergence of anticholinergic therapy, timed voiding, and behavior modification then began playing a larger role in the treatment of dysfunctional voiders [4].

Later in the 1980s, van Gool again began refocusing on urinary flow patterns and the external sphincter. He redefined the term "voiding dysfunction" to refer to only patients with abnormalities of urine flow. He also linked sphincter contraction with voiding to recurrent urinary tract infections and vesicoureteral reflux [32]. Most refer to this as "secondary" reflux, which is caused by bladder obstruction and the elevated bladder pressures that accompany it. Secondary reflux has both functional (dysfunctional voiding) and anatomic components (i.e., posterior urethral valves). At the same time, Koff et al. described the correlation between constipation and urinary symptoms, referring to "dysfunctional elimination syndrome" as one of the underlying components of dysfunctional voiding. This syndrome, encompassing both the urinary and gastrointestinal systems, also can obviously lead to recurrent urinary tract infections and vesicoureteral reflux [19, 20].

During this time of identification of the causes of dysfunctional voiding, Sugar and Firlit introduced the use of biofeedback in the treatment of incontinence and recurrent urinary tract infections. They describe inpatient biofeedback lasting 24–48 hours that taught children to convert a dyssynergic voiding pattern to a synergic one, with an 80% success rate [31]. Hellstrom et al. then reported on their experience with a bladder rehabilitation program that utilized both timed voiding and a biofeedback program which had up to a 3-year duration. They found an 87% improvement rate in the voiding patterns of the 70 children that were treated [12]. Currently, there are numerous pediatric centers which have a multi-disciplinary team approach whose main focus is pelvic floor therapy.

22.3
Diagnosis of a Dysfunctional Voider

Initial evaluation of patients with incontinence or urinary tract infections includes a complete history to determine the pattern of incontinence, associated problems, and family history. Important questions to ask include the duration, quality, and frequency of the symptoms, as well as timing and whether or not the patient has displayed signs of dysfunctional voiding. Some of these signs include postures that provide external compression or forceful contraction of the pelvic floor to prevent urination, such as crossing their legs (the "pee pee" dance) or squatting with one foot against the perineum ("St. Vincent's curtsey" or "squatter" sign). Physical examination includes inspection of the spine, the sacrum, the genitalia, and a basic neurologic exam [33]. When examining the base of the spine, specific attention should be made to whether of not a tuff of hair, fat (lipoma), dyssymetry, or blind ending sacral dimple is present. If any of these are present, then an MRI study should be done to rule out the presence of a neurologic lesion [34]. Urinalysis and urine culture is the only laboratory investigation that is necessary.

Routine urologic testing is recommended to rule out anatomic causes for incontinence or urinary tract infection, starting with renal ultrasound with a full and empty bladder and a voiding cystourethrogram, at least in those cases with a history of infection. The full scope of anatomic causes will not be discussed here since the main focus of this chapter is the use of pelvic floor therapy in cases with no anatomic abnormalities. Some causes include neurologic lesions such as those found in chil-

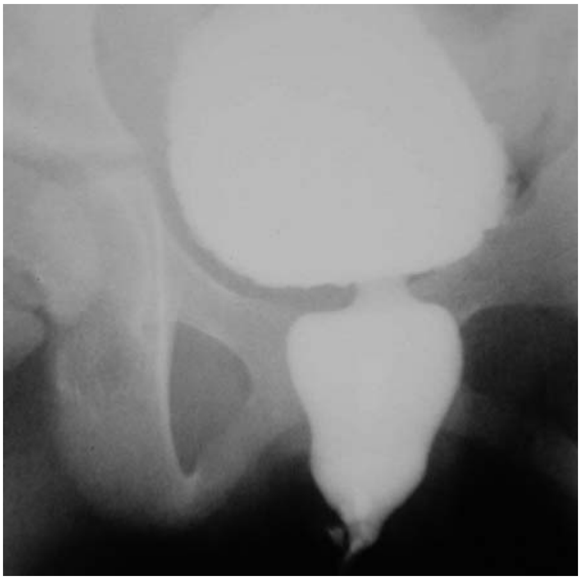

Fig. 1. Spinning-top deformity on voiding cystourethrogram

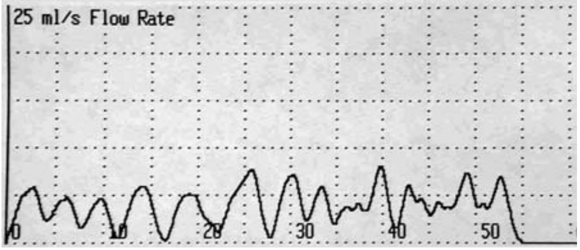

Fig. 2. Staccato uroflow tracing of a dysfunctional voider

dren with spina bifida or anatomic abnormalities such as posterior urethral valves in boys. Findings on voiding cystourethrogram that are indicative of dysfunctional voiding include spinning top deformity, trabeculation, thickened bladder wall, or a significant postvoid residual (Fig. 1) [9].

Another component of the diagnosis is urodynamic testing in order to objectively prove dysfunctional voiding. Most pediatric urologists will not perform invasive urodynamic study until there is failure of behavior modification or there are other findings suggestive of a neurological component to the symptoms. This is because in reality it is often difficult to obtain reliable urodynamics in the pediatric population. Another reason to not perform urodynamics initially is that it avoids yet another test for the patient to have to go through to prove a diagnosis that could likely be corrected with simple behavior modifications and pelvic floor therapy. The gold standard of urodynamic evaluation is videourodynamics since voiding and the bladder neck is visualized in real time [11].

At the onset of treatment, we recommend obtaining a noninvasive uroflow study with electromyography (EMG), which simultaneously records urethral urinary flow and voluntary striated sphincter/pelvic floor. This not only provides objective evidence of noncoordinated voiding, but it also gives a baseline for which to judge improvement, or lack thereof, after biofeedback therapy. A specific clue of dysfunctional voiding on uroflow strips includes evidence of DSD such as a staccato voiding pattern (Fig. 2) [31]. While more than 75% of dysfunctional voiders display bladder instability, this is not diagnostic; however, when bladder instability is combined with signs of impaired or obstructed emptying, such as low flow rate, high residual volume, and/or high intravesical pressures in the absence of neurologic disease, the diagnosis of dysfunctional voiding is highly suggested [4]. Regardless of whether or not formal invasive urodynamics is done first, behavior modification and pelvic floor therapy are the first- and second-line treatments in children with dysfunctional voiding.

22.4
Treatment of a Dysfunctional Voider

After ruling out organic causes of incontinence and urinary tract infection, we usually recommend starting with simple behavior modification as pelvic floor therapy is being initiated. Most centers combine timed voiding and increased fluid intake, along with special tricks to improve voiding. McKenna and McKenna describe adding Cheerios, the breakfast cereal, to the toilet bowl and having children try to sink them to encourage emptying and relaxation [23]. Elimination (voiding and stooling) diaries are encouraged to help ensure patient compliance, as well to help keep parents aware and involved. Constipation is often a concomitant problem and usually behavior modification for urinary symptoms includes an aggressive bowel regimen if indicated [10]. In one study, 89% of daytime incontinence, 63% of nocturnal enuresis, and all urinary tract infections (in children who had no abnormalities present) resolved with treatment of constipation [21].

Besides timed voiding and simple relaxation techniques, the other component is avoidance of certain foods that can induce bladder instability such as caffeine, citrus, carbonation, and chocolate (the “four Cs”). Usually, behavior modification helps to improve urinary symptoms of incontinence and urinary tract infections; however, learned behavior is difficult to change. Along with behavior modification, we recommend instituting pelvic floor therapy, utilizing biofeedback techniques. Invariably, bladder retraining is recommended for the ultimate goal of achieving a cure.

While treatment is underway, anticholinergic therapy can also be used to help alleviate symptoms, as well

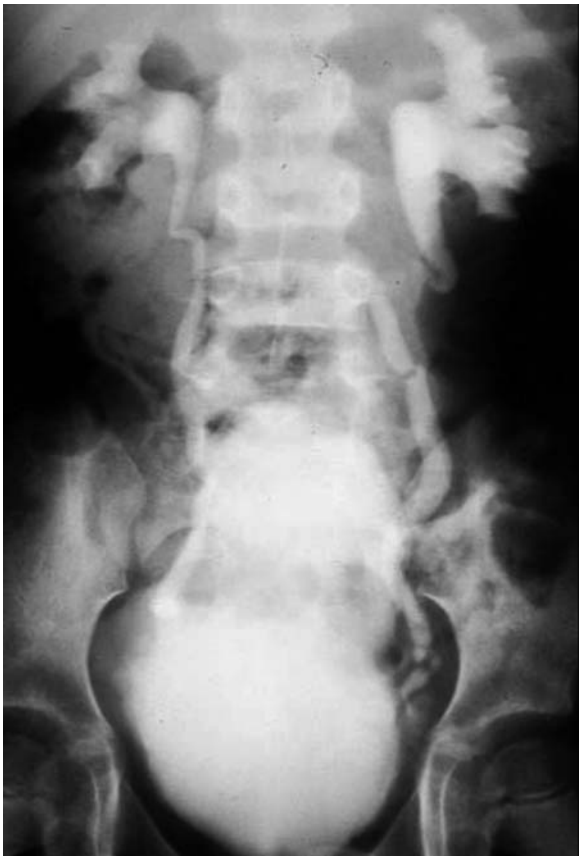

Fig. 3. Voiding cystourethrogram demonstrates vesicoureteral reflux resulting from dysfunctional voiding

as help decrease high bladder pressures of those with severe dysfunctional voiding with poor bladder compliance and evidence of uninhibited contractions. Clean intermittent catherization may also be required in more end-stage cases for those children who no longer can empty their bladder well [4]. While behavior modification and pelvic floor therapy are being instituted, prophylactic antibiotics are indicated in those patients with vesicoureteral reflux, febrile urinary tract infections, or recurrent cystitis. Surgical options, such as endoscopic reflux correction or open ureteral reimplantation for those with vesicoureteral reflux, are other options prior to pelvic floor therapy if compliance with antibiotic prophylaxis or breakthrough UTIs are an issue (Fig. 3). The success rate of surgery in this subgroup of patients is lower than traditional outcomes, but it is a way to protect the upper tracts in those who are at high risk for infection and venal scarring while pelvic floor therapy is being instituted. For example, Soygur et al. looked at a population of dysfunctional voiders as diagnosed by urodynamics studies and found that 26% of the patients who underwent bilateral ureteral reimplantation still had persistent vesicoureteral reflux postoperatively [30].

22.5
Anatomy and Physiology of the Pelvic Floor

In order to understand how pelvic floor therapy works, one must understand the anatomical components of the pelvic floor as well as the physiology of micturition. The pelvic diaphragm, also known as the levator ani, supports and stabilizes the bladder, uterus, and bowel. It is composed of three muscles: the pubococcygeal, the iliococcygeal; and the ischiococcygeal, which is also known as the puborectalis. These muscles form a “bowl” in the pelvis, attaching to the obturator tendon, pubis, sacrum, and the inner surface of the pelvis. The sling or bowl created by the muscles has a relatively high tone at rest and it is this constant tone at rest that helps to keep the bladder outlet closed until micturition begins. With contraction of the pelvic diaphragm, there is also increased support and stabilization of the bladder and bowel, along with improved closure of the urethral and anal sphincters [15].

The group of muscles that interdigitates the pelvic diaphragm, as well as external anal sphincter, is known as the urogenital diaphragm. This is also composed of three muscles and it includes the transverse perineal, the bulbospongiosus (or bulbocavernous), and the ischicavernous muscles. They attach to the symphysis pubis, pubic rami, the perineal rami, and the ischial tuberosities. The other skeletal muscles important in biofeedback exercises include the breathing diaphragm, the external sphincter, obturator internus, the adductors, and the abdominal muscles [15].

Bladder control and micturition involves complex interactions between the somatic (voluntary) and autonomic (sympathetic and parasympathetic) parts of the nervous system. The somatic nerves from the sacral cord course through the pelvic plexus and the pudendal nerve to innervate the skeletal muscle component of the external urethral sphincter. The somatic nerves also innervate the pelvic and urogenital diaphragm via the pudendal nerve, allowing one to voluntarily contract and relax these muscles. The pelvic and urogenital diaphragm tightens by pulling up and in, like a hammock or sling, in order to prevent leakage during heavy physical activity or when there is a need to urinate but, for whatever reason, one wants to prevent micturition. The fact that this group of muscles is under voluntary control is the basis for pelvic floor therapy because it “teaches” patients to voluntarily relax their urogenital diaphragm as well as their external urethral sphincter.

The autonomic component of the central nervous system comes from thoracic nerve roots 10 through lumbar 1 (sympathetic) and sacral nerve roots 2 through 4 (parasympathetic) [3]. The sympathetic nervous system is responsible for the storage phase by relaxing the detrusor muscle during filling, allowing for compliance of the bladder wall and thereby leading to bladder filling at low pressures. Sympathetic innervation also controls the bladder neck and the proximal urethra, causing contraction of the internal urethral sphincter. Once bladder capacity is reached, one of the many reflex pathways causes deactivation of the sympathetic nervous system and allows the parasympathetic system to take over. Normally inhibited by the sympathetic system, the parasympathetic nervous system can now initiate relaxation of the internal urethral sphincter and contraction of the detrusor muscle, causing emptying of the bladder [1].

All of the phases of the bladder (storage, filling, emptying) are governed by a complex process that involves several centers within the brain, various levels along the spinal cord, the intrinsic properties of the bladder and the posterior urethra, and the striated muscle component of the external sphincter [3]. That is to say, bladder function is a combination of multiple reflex pathways, the voluntary nervous system, and the autonomic nervous system.

In basic terms, normal micturition begins with the sensation of fullness and the desire to void, followed by relaxation of the striated sphincter, and then initiation of voluntary bladder contraction. The bladder neck relaxes creating a coordinated event where bladder and urethral pressures are equal. At the end of voiding, urethral pressure rises again and the sphincter closes to maintain continence. During the storage phase, bladder pressure remains lower than the pressure inside the urethra so that the bladder neck remains closed, thus maintaining continence. As the filling phase begins, the bladder pressure should remain essentially unchanged throughout, indicating good compliance [1].

Dysfunctional voiders often hold urine for prolonged periods of time, and, therefore, the action of external sphincter contraction to prevent urinary leakage becomes habitual. This leads to bladder instability, as well as contraction of the external sphincter even during voluntary voiding. Other children likely cannot relax while voiding leading to the same eventual sequelae characteristic of obstruction such as increased residual urine, high intravesical pressures, and problems such as incontinence and recurrent urinary tract infections [3]. Another theory is that some pediatric patients still lack maturity of their voiding reflex pathways, making them unable to centrally inhibit detrusor contractions thereby causing them to habitually use their external sphincter to prevent leakage. This action can also lead to bladder instability and the inability to relax the external sphincter during voiding.

22.6
Pelvic Floor Therapy

Pelvic floor therapy is second line treatment for dysfunctional voiding, after behavior modification. The technique of cognitive relearning is also known as "biofeedback therapy" and "bladder retraining" [32]. As mentioned, biofeedback is any method of training that teaches a patient to control a bodily function by providing him or her with information about that function. This information can be relayed to the patient verbally, from digital feedback after examination, through the sensation of vaginal cones, or with mechanized equipment emitting audio or visual signals that correlate to the function [34].

Pelvic floor muscle contraction and relaxation is not an action normally perceived by an individual. Biofeedback enables an individual to become aware of these muscles at a conscious level. Dysfunctional voiders often have chronic inappropriate contraction of the pelvic floor during voiding, resulting in bladder muscle thickening and bladder hyperactivity. By teaching patients how to control pelvic floor muscles, patients can learn relaxation and this ultimately results in improved flow and emptying. In most patients, reversal of the negative effects on the bladder will occur with time as voiding improves [23].

The goals of pelvic floor therapy include the development of muscle awareness and isolation and the utilization of this learning in everyday life. Pelvic floor therapy is presently done on an outpatient basis, as compared with the initial programs 20 years ago where inpatient hospitalization was required for 24–48 hours [31]. Some early institutions in Europe began with an intensive 10 day inpatient treatment program [33]. While there are many examples of treatment programs, we use the pelvic floor therapy model as described by Herndon et al. to outline the basic steps that should be included in a successful pelvic floor therapy program [13].

After elimination education has been completed, such as the behavior modifications mentioned above, a noninvasive uroflow study with EMG is performed. This not only provides objective evidence of dysfunctional voiding, but it also gives a baseline for which to gauge improvement, or lack thereof, throughout the treatment program. The patients then meet with a therapist to learn muscle retraining using a standard biofeedback system (e.g., the Self-Regulation Systems, Seattle, Washington). The initial visit usually lasts 1 hour and also serves as an introduction to both parent and patient. Follow-up biofeedback sessions should start with a review of what was done on the previous visit, assessment of the patient's compliance of home exercises, and questioning of changes in incontinence, constipation, and whether or not recurrent urinary tract infections have occurred in the session interval. Also all questions and concerns should be addressed prior to initiation of biofeedback therapy [13].

The basic set-up of pelvic floor therapy begins with placement of surface electrodes at the 3 and 9 o'clock positions on the perineum, which measure the electrical

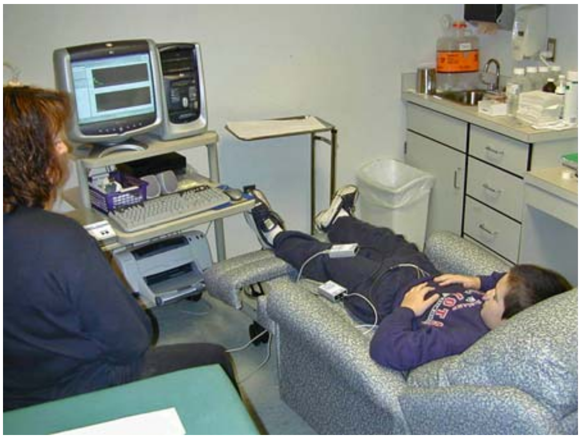

Fig. 4. Patient and therapist in a biofeedback training session

activity of the pelvic floor muscle group. An additional surface electrode is placed on the rectus abdominus muscle to record abdominal muscle activity. Afferent leads are then connected to an external device that interprets the electrical activity of the pelvic floor and abdominal musculature. The external device is then connected to a parallel port on the computer which corresponds to a visual image on the computer screen (Fig. 4). Herndon et al. also describe the use of interactive computer games along with pelvic exercises, entitled “biogames,” to help aid in pelvic floor exercises, retraining as well as to sustain patient interest. These games are controlled by the EMG activity of the pelvic floor [13].

After the biofeedback system is in place, Kegel exercises and short bursts of pelvic floor contraction (“quick flicks”) are used to isolate the pelvic floor muscles. This action of pelvic floor isolation is confirmed by visual feedback of increased pelvic floor muscle activity in the absence of EMG activity of the abdominal electrode. Once this muscle group is isolated, the next step is learning relaxation of the pelvic floor muscles. Once this is achieved, the final portion of the session is used for reinforcement. If using the interactive “biogames,” then the patient will end the session playing the games for reinforcement. Patients who have difficulty in isolation should be given immediate instruction with techniques in order to achieve pelvic muscle control. Between sessions, the patient is given homework consisting of specific exercises, as well as the task of updating their voiding diary to monitor incontinence and constipation [23].

Pelvic floor therapy usually requires six to ten sessions to learn how to isolate and relax the pelvic floor muscles. Improvement parameters include a decrease in the number of incontinence episodes and urinary tract infections, resolution of vesicoureteral reflux, and more objective improvement such as more coordinated voiding noted on uroflow/EMG. The active biofeedback sessions can be terminated after the patient shows consistent pelvic floor relaxation during voiding at two sessions, along with clinical improvement. Some also offer a follow-up session 6 months after the completion of therapy for reinforcement purposes, as well as to ensure continued compliance [7].

While the International Children’s Continence Society (ICCS) has standardized and defined lower urinary tract dysfunction in children, there is no agreement as to the optimal form of pelvic floor therapy in children. Inpatient versus outpatient and group versus individualized therapy have all been attempted. Schulman et al. [28] looked at two different methods of performing pelvic floor therapy. One method was one day of intensive treatment with a small group of children to induce camaraderie, while the other method was composed of 60-min sessions on a one-to-one basis. Their study found no significant difference in the two methods; however, it was not a randomized study. Whatever the method or the type of session, most agree that patient compliance and cooperation are essential [28].

22.7
Success Rates of Pelvic Floor Therapy

The fundamental components of successful pelvic floor therapy are patient participation and motivation. Without them, it is impossible for success. Most studies quote a success rate, meaning significant improvement in symptoms, of approximately 80–95% for pelvic floor therapy. In terms of “cure,” Kjolseth quotes 56% with 24% of patients that have a decrease in urinary symptoms [18]. McKenna and McKenna found a 90–95% decrease in recurrent infections without the use of long-term prophylactic antibiotics using a systematic approach to treating children with recurrent urinary tract infections and dysfunctional voiding, including timed voiding, hygiene, and aggressive treatment of constipation with associated pelvic floor muscle retraining [23]. For secondary vesicoureteral reflux caused by dysfunctional voiding, success rates in the resolution of reflux with biofeedback therapy are approximately 55% and improvement in an additional 16% according to Palmer et al. [25].

Most other studies agree that pelvic floor therapy is highly effective, as long as patient motivation and commitment is present [7]. Porena et al. found that overall success of biofeedback therapy was 87% at 2 years and 80% at 4 years [27]. Combs et al. found 81% of patients had an excellent response, 14% had a fair response, and 5% that were too inconsistent in therapy to rate. The average number of sessions in their study to achieve a consistent urodynamic response was 3.7 (range 2–14); however, the majority of these patients averaged about 6 months for significant or complete symptom resolution [9].

Since pelvic floor therapy is dependent on the participation of the patient, a number of investigators have studied its efficacy in the younger population. Some studies have found that children less than 5 years old are not good candidates for biofeedback because of lack of cooperation and increased anxiety [16]; others, however, disagree. Hellstrom et al. was one of the few groups to report that biofeedback training was applicable in children 4–5 years of age [12]. This was reiterated by De Paepe et al., who felt that the most important factor was maturity and that in the younger age group extra motivation and explanation is required in order to achieve the equivalent success rates [10].

While patient motivation and compliance are essential for success, there is another main risk factor of pelvic floor therapy failure. Herndon et al. report that a small-capacity bladder, specifically referring to voided volume plus postvoid residual that was 70% or less predicted bladder capacity, is a predictor of failure as well as noncompliance. In the subgroup of patients that had pelvic floor therapy failure, a trial of anticholinergic therapy is recommended in those with small bladder capacity and a low postvoid residual to determine if there is any improvement in symptoms [13]. Alpha-adrenergic blockade can be tried in patients with biofeedback failure and flattened flow pattern with minimal pelvic floor activity, which can be indicative of primary bladder neck dysfunction. McKenna and Herndon also state that pelvic floor therapy failure when not attributed to noncompliance can be an indication to perform a complete urodynamic evaluation. This is usually required in less than 5% of patients that initially present with dysfunctional voiding, whereas less than 10% eventually required medication. Most authors also recommend obtaining more extensive imaging, such as magnetic resonance imaging, to rule out occult neurological abnormalities in those in whom pelvic floor therapy is not successful [22].

22.8
Role of Pelvic Floor Therapy Today

Many urology practices and their institutions are now describing comprehensive centers that are devoted to the treatment of the dysfunctional voider. One example is at the Children's Hospital of Philadelphia where a multidisciplinary approach is used to not only treat patients, but also to keep parents fully informed and up to date. The staff at the center includes a pediatric urologist, pediatric nephrologist, psychologist, and two nurse practitioners. Schulman et al. retrospectively reviewed 280 patients that underwent various types of therapy, including antibiotic prophylaxis, anticholinergic medication, biofeedback, and psychological counseling, depending on the patient's individual problem. Pelvic floor therapy was used for patients that demonstrated bladder and/or sphincter dysfunction. They found that 45% of those with daytime wetting were cured and another 37% were improved. Of those with recurrent urinary tract infections, 64% had no subsequent infections. This comprehensive approach not only helped improve clinical symptoms, but it also minimized psychological morbidity, which is often seen in patients with dysfunctional voiding [29]. Many other centers across the country use this model, incorporating pelvic floor therapy as the mainstay of treatment for dysfunctional voiding.

22.9
Conclusion

Pelvic floor therapy plays a major role in the treatment of dysfunctional voiding. It is a noninvasive form of therapy that both resolves urinary symptoms and corrects the underlying disorder, in hopes of achieving long-term cure. Pelvic floor therapy is a teaching tool that helps to correct the “dysfunction” of voiding with a success rate ranging from 80 to 95% in improving incontinence. It also decreases recurrent urinary tract infections and decreases the need for surgical intervention for vesicoureteral reflux. Biofeedback therapy can also be used in conjunction with other types of treatment such as behavior modifications, medication, and/or surgical correction. In pediatric urology, its primary role is in treating and improving the neurologically normal group of children with evidence of dysfunctional voiding.

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23

Sacral Nerve Stimulation

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23.1
Introduction

Neurogenic bladder dysfunction in children can involve a variety of etiologies including congenital defects, such as spina bifida, sacral agenesis, and spinal dysraphism, with or without tethered cord and/or lipoma or other causes such as tumor or trauma. Regardless of underlying pathophysiology, neurogenic bladder dysfunction often leads to progressive bladder and upper urinary tract deterioration [1, 2].

Medical treatment is based mainly on anticholinergics, antibiotics in case of associated urinary tract infection, and intermittent catheterization. It can and often is associated with surgical treatment of varying invasiveness including periurethral injection, bladder neck reconstruction, artificial urinary sphincter implantation, and augmentation cystoplasty.

The development of systems for electrical stimulation of the neurogenic bladder coincided with a better knowledge of the pathophysiology of neurogenic bladder dysfunction. In patients with complete spinal cord injury and bladder hyperreflexia, the complete micturition cycle must be controlled. This means that supplementary to electrostimulation for evacuation, an increase in bladder capacity and compliance must be realized. Two approaches for stimulation of the bladder in patients with, for example, spinal cord injury, are available, one of which is intradural and the other extradural.

Brindley from London started with animal experiments with the purpose of developing a system for intradural sacral anterior root stimulation in 1969 [3]. The first successful sacral anterior root stimulator for a patient with traumatic paraplegia was implanted in 1978 [4]. The clinical results have been largely improved since the introduction in 1986 of complete intradural sacral posterior root rhizotomies to control the reservoir function of the bladder in combination with implantation of the sacral posterior root stimulator [5].

Another type of sacral root stimulation for the evacuation of urine in spinal cord injury was developed by the San Francisco group of researchers. As a result of their research, electrodes were placed extradurally in combination with selective posterior rhizotomies of S3 and/or S4 sacral roots. The extradural approach has separation of the anterior and posterior part of the sacral roots is more difficult in the extradural segment of S3 and nearly impossible at the S4 Level [6].

During the past few decades, functional electrical stimulation has gained interest in the treatment of lower urinary tract dysfunction. Different stimulation sites, such as the vagina or the anus, have been reported to be successful. Since the 1960s, transcutaneous neurostimulation applied to the third or fourth sacral foramen has been tried as a method to control functional lower urinary tract disorders in the adult population [7]. Unilateral sacral segmental stimulation with a permanent electrode at the level of the sacral foramen S3 or S4 (so-called sacral nerve stimulation: SNS or interstim therapy) can offer an alternative nondestructive mode of treatment for patients presenting with voiding dysfunctions refractory to conservative measures.

23.2
Sacral Nerve Stimulation

23.2.1
Efferent Pathways

The pelvic floor musculature receives a major part of its innervation via the pudendal nerve. Nerves branching to the urethral sphincter and levator ani muscle divert proximally before the pudendal nerve reaches the ischiosacral ligament. Approximately 70% of external urethral sphincter pressure is dependent upon efferent activity in the S3 ventral root, whereas S2 and possibly S4 contribute the remaining 30% [8].

Sacral parasympathetic preganglionic fibers that travel in the pelvic nerve provide the major excitatory input to the urinary bladder. Preganglionic axons project to ganglion cells on the surface of the bladder. Parasympathetic ganglion cells in the bladder provide an excitatory input to the detrusor smooth muscle via the release of predominantly cholinergic transmitter.

Sympathetic pathways that originate in the thoracolumbar segments of the spinal cord provide inhibitory input to the bladder and an excitatory input to the bladder neck and proximal urethra [9].

23.2.2
Afferent Pathways

The micturition reflex requires not only efferent pathways from the spinal cord to the urinary bladder but also afferent input from receptors in the bladder to the spinal cord. Integrity of afferent nerves is critical for sending signals of bladder fullness and discomfort to the brain and to initiate the micturition reflex. Somatic afferent pathways from the perineal area transmit information that can make the patient aware of the surrounding environment and warn him if there are noxious stimuli or if there is tactile sexual pleasure to his genital region.

23.2.3
Bladder Hyperactivity and Urinary Incontinence

Bladder hyperactivity and urinary incontinence are assumed to be mediated by the loss of voluntary control of voiding and the appearance of primitive voiding reflux circuitry. This can occur as a result of the re-emergence of neonatal reflex patterns that were suppressed during postnatal development or the formation of new reflex circuits mediated by C-fiber afferents; under normal conditions the latter are through to be mechano-insensitive and unresponsive to bladder distension but as a consequence of neurological and inflammatory diseases. In theory, this type of bladder hyperactivity could be suppressed by blocking C-fiber afferent activity or by interrupting reflex pathways in the spinal cord.

23.3
Mechanism of Action: Sacral Nerve Stimulation

The hypothesis is that SNS depends on electrical stimulation of afferent axons in the spinal roots which in turn modulate voiding and continence reflex pathways in the central nervous system. The afferent system is the most likely target because beneficial effects can be elicited at intensities of stimulation that do not activate movements of striated muscles [10]. Moreover, SNS can elicit similar responses in patients with urinary retention and turn off excitatory outflow to the urethral outlet and promote bladder evacuation. Sphincter activity can generate afferent input to the spinal cord that can in turn inhibit reflex bladder activity. A benefit of suppressing sphincter reflexes would be a facilitation of bladder activity.

Different reflex mechanisms are involved in the SNS suppression of bladder hyperactivity. It is known that various afferent pathways projecting to the sacral cord can inhibit bladder reflexes in animals and humans. The list includes afferents from the pelvic floor and sphincter muscles, afferents from the distal colon, rectum, and anal canal, afferents from the vagina and uterine cervix, and cutaneous afferents from the perineum.

The principles behind SNS can thus be summarized as somatic afferent inhibition of sensory processes. Pudendal afferent input to the sacral spinal cord can turn off supraspinally mediated hyperactive voiding, blocking the ascending system. Pudendal afferent input can also turn on voiding reflexes by turning off the guarding pathways [8].

The concept of SNS (interstim therapy) differs from that of neurostimulation developed by Brindley and Tanagho [13]. The main advantage of the neuromodulation technique is reversibility. Association with anterior rhizotomy is unnecessary [10].

23.4
Technical Considerations

23.4.1
The Implantable System

The implantable system is composed of a neurostimulator, an extension cable, and a lead with quadripolar electrodes (Medtronic, Minneapolis, Minn.). The electrode is implanted in one of the sacral foramen, typically at the level of S3. The neurostimulator is implanted subcutaneously in a lower quadrant of the abdomen in the young patient or posteriorly at the upper buttock region if this

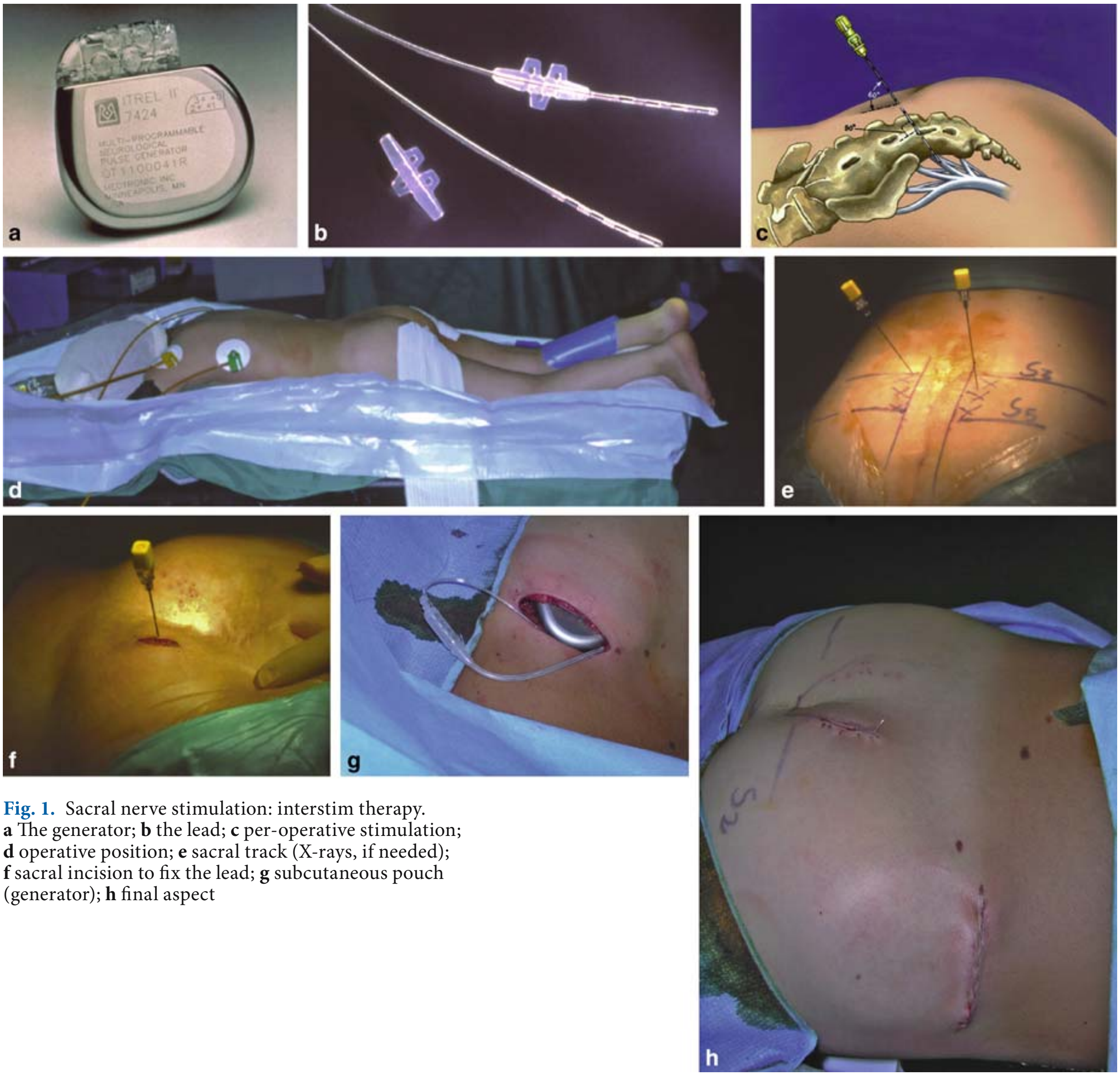

Fig. 1. Sacral nerve stimulation: interstim therapy. **a** The generator; **b** the lead; **c** per-operative stimulation; **d** operative position; **e** sacral track (X-rays, if needed); **f** sacral incision to fix the lead; **g** subcutaneous pouch (generator); **h** final aspect

localization can be supported by the patient anatomy (older children; Fig. 1). The physician uses an electronic device (medical programmer) to adjust the parameters of electrical stimulation produced by the neurostimulator. An external patient programmer is used by the patient to run the stimulator on and off and to increase or decrease the level of stimulation.

23.4.2
Implant Procedure for the Foramen Lead

Under general anesthesia without any curare, after careful skin preparation, the patient is positioned prone on the operating table with the hips and knees folded so as to present the sacral region as horizontally as possible. A test stimulation is performed to confirm stimulating electrode placement using evoked muscle responses as a guide by an insulated 20-G needle was used to locate the appropriate sacral foramen percutaneously. The S3 nerve was located by moving the needle and gradually increasing the intensity of stimulation until the desired response (anal contraction or plantar flexion of the great toe) was obtained. Bilateral testing was performed in order to determine which side gave the best response.

A vertical incision over the sacrum is then made down through the fascia on the side that produced the best response. Muscles are separated to access the foramen. Acute testing may be repeated to confirm responses and the quadripolar lead is inserted into the selected foramen. Test stimulation of the electrodes on the lead is again performed to determine that appropriate responses are obtained prior to lead fixation to the body. After the lead is positioned, lead anchors are fixed to the sacral periosteum or bone to secure the lead in place. A trocar is used to create a subcutaneous tunnel to the patient's flank, where a small incision is made. The lead and extension cable are connected later.

The patient is repositioned for implantation of the neurostimulator. A pocket is made for it in a lower quadrant of the abdomen, between the muscle fascia and the subcutaneous fat. Using a tunneling tool, the extension is tunneled under the skin in the direction from the abdominal incision to the flank incision. At the flank incision, the extension is connected to the lead. The other end of the extension is then connected to the neurostimulator. Excess length of extension is pulled into the abdominal pocket, coiled up, locked under the neurostimulator, and secured with sutures. The neurostimulator is fixed in place and the system is then tested to confirm correct device function after wound closure.

Stimulation is normally activated on the day following surgery using the most effective electrode position of the four electrodes. For initial activation each of the four separated electrodes is tested and the electrode providing the best response is set as the cathode (-) and the case as the anode (+). Pulse width is generally set at 210 µs, and the pulse rate at 10 pulses per second, at an amplitude of 0.1 V. Pulse amplitude should be increased slowly, in increments of 0.1 V until the subject senses stimulation and/or pelvic floor muscle responses are obtained. While determining threshold voltages for the various electrodes, impedance values for the electrodes should be determined. The electrode with the lowest threshold is often the most effective for long-term stimulation. It is noteworthy that the electrical threshold can vary not only with regard to the patient's sensory and motor responses, but also with regard to the comfort and therapeutic responses. Evaluation of stimulus parameters should be performed while communicating and receiving appropriate feedback from the patient. Feedback from the patient includes electrical sensation, pain, and muscle contractions.

From a purely technical standpoint in our pediatric population with neurogenic bladder, pulse width, amplitude, and sometimes frequency settings are adjusted in accordance with motor response, since most patients present extremely altered or no perineal sensibility. Adjustment is almost always necessary to maintain constant motor response, probably due to a decrease in electrical diffusion caused by mild migration of the lead or fibrous membrane formation around it.

23.5
Discussion

Numerous studies in adults presenting indications as diverse as urinary retention and refractory urge incontinence have shown that SNS (interstim therapy) can inhibit unstable nerve reflexes and restore normal micturition [11–19]; however, only one study (from our team) has been published to evaluate interstim therapy in children or adults with congenital neurogenic bladder. It was a prospective randomized study designed to evaluate the middle- and long-term efficacy of neuromodulation in children with neurogenic bladder dysfunction [20]. Efficacy was evaluated by comparing clinical and urodynamic results in an implant and control group as well as by evaluating interindividual variations in comparison baseline.

A total of 42 patients, including 26 boys and 16 girls with a mean age of 11.9 years (range 5–21 years), were enrolled in this study over a period of 33 months. There were 21 patients (13 boys and 8 girls) in each group. In the control group, spina bifida was the underlying etiology for all but 1 patient who presented neurogenic bladder secondary to meningoencephalitis. In the implant group, the underlying etiology was spina bifida in 13 cases, partial sacral agenesis in 2, trauma in 2, tumor in 2, neonatal cerebral palsy in 1, and urofacial syndrome in 1 case.

Various treatments had been used prior to inclusion in this study. Of the 21 patients in the control group, 15 had been treated by anticholinergics, 10 had one or more endoscopic injections (Macroplastic) in the bladder neck, and 3 had already been undergone bladder surgery (temporary neonatal tubeless cystostomy and Young Dees). Of the 21 patients in the implant group, 10 had been treated with anticholinergics, 3 had Macroplastic injection in the bladder neck and 1 patient had a Mitrofanoff procedure.

Statistical analysis of the two patient groups at inclusion demonstrated no difference with regard to gender, median age and urodynamic variables, i.e., compliance, functional bladder capacity, bladder filling, leak-point pressure, bladder activity, and post-voiding residue.

In the implant group, the neurostimulator was placed above the waistline on the left or right side of the anterior abdominal wall in 8 cases and in the upper buttock region in 13 patients. Revision surgery was required in 3 cases due to lead migration, faulty connection, and superficial wound infection. No other complications were noted. Neuromodulation was the only therapy used in 9 cases and was associated with intermittent catheterization in 12 cases.

All patients in the control group were treated with anticholinergics (Driptane). Dosage was adjusted according to age with a maximal dose of 15 mg/day. In addition to anticholinergics, 15 patients required intermittent catheterization and 8 patients underwent macroplastic injection in the bladder neck.

Total disappearance of urinary leakage was observed in 1 patient who underwent implantation, but he still required intermittent catheterization.

Comparison of urodynamic variables at each study time disclosed no statistically significant difference between the implant and control groups with regard to compliance, bladder filling pressure, and post-voiding residual. A significant increase ($p<0.05$) in leak-point pressure was noted in implant patients at 3, 6, 9, and 12 months. Conversely, at the end of the study functional bladder capacity was significantly greater in the control group. Electromyographic activity was difficult to interpret due to high variability and, as a result, was not studied.

Evaluation of interindividual variations in the implant group disclosed that compliance and functional bladder capacity were significantly higher at 6 and 9 months, but not at 12 months. Total bladder capacity also increased significantly; however, there was no measurable improvement in bladder filling pressure and post-voiding residue.

Nine patients in the implant group reported an improvement in intestinal transit (evaluated from diary data), 5 reported total disappearance of urinary infection, and 6 patients reported sensation of full bladder. No patient in the control group reported subjective improvement.

23.6
Conclusion

Sacral nerve stimulation (interstim therapy) in children seems to be a promising new therapeutic modality. Implant placement is minimally invasive, non-destructive, and reversible. Use in children with neurogenic bladder is only at the beginning stages. Our results are encouraging, but the study population was too small, and the lesions were probably too severe to demonstrate the benefit of this therapy. A French multi-center study, including more patients with less severe lesions, has been under way since April 2005.

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Botulinum Toxin Injections to Treat Neurogenic Bladder – Sphincter Dysfunction in Pediatric Patients

24

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24.1
Introduction

Most paediatric cases of neurogenic bladders are encountered in children with myelomeningocele (MMC), tethering of the cord or sacral anomalies. In most cases the anatomical defect is apparent at birth. Only occasionally children with tethering of the cord come later to the attention of the physician with minor defects, such as spina bifida occulta, slight skin discoloration and abnormal hair growth, or a sacral dimple associated with gait disturbance, incontinence or recurrent urinary tract infections.

Detrusor sphincter dyssynergia is a major urological problem in newborns with MMC and occurs in almost 50% of them [1]. At birth, the majority of these patients have a normal upper urinary tract. Natural history shows that hydro-ureteronephrosis develops in 72% of MMC patients with detrusor sphincter dyssynergia, and vesicoureteral reflux is found in about 81% of patients with a leak-point pressure of 40 cmH_2O or more [1, 2]. Treatment of the bladder dysfunction is therefore aimed primarily at preservation of the upper urinary tract. Management goals are directed at building a low-pressure reservoir with regular emptying (in the first years of life), whereas later, as the child grows up, continence promotion is added to improve quality of life.

Significant advances in the diagnostic approach and treatment of children with incontinence secondary to detrusor–sphincter dysfunction have been based on progress in urodynamics, introduction of early clean intermittent catheterization and pharmacotherapy of the overactive detrusor.

24.2
Diagnosis

In children with bladder dysfunction, the detrusor may be normal, overactive or inactive. The urethral sphincter may be normal, overactive or paralysed. These conditions may exist in any combination [3, 4]. Symptoms such as urgency, frequency and urge incontinence are sometimes associated with stress urinary incontinence. In other cases, symptoms of urinary infection or upper tract infection reveal the dysfunction. Urodynamic evaluation (ideally video-urodynamic) makes pattern recognition possible and helps to establish a management plan for each patient. In general, the combination of an overactive detrusor and sphincter is potentially the most dangerous because of high intravesical pressures, putting the upper tract at risk, whereas an inactive detrusor or a paralysed sphincter, providing a low-pressure reservoir, is relatively safe.

24.3
Management and Treatment of Neurogenic Overactive Bladder

The management of MMC patients has to start early. In the first days of life, hydronephrosis or reflux must be eliminated using ultrasound and voiding cystogram. If any of these images reveal abnormalities, or if the bladder does not empty properly, early intermittent catheterization must be proposed. Recurrent infections could also be an indication of the early need for intermittent catheterization. Urodynamic testing could help to measure resting and detrusor leak-point pressure. These parameters assist in deciding on anticholinergics or intermittent catheterization. In rare cases of significant hydronephrosis or massive vesico-ureteral reflux, vesicostomy could be considered.

In older children, ultrasound and urodynamics, in conjunction with evaluation of leakage episodes and recurrent infections, are key elements for adequate management. In most cases basic treatment is composed of intermittent catheterization and increasing doses of anticholinergics: primarily oxybutinin [5, 6]. Failure of that conservative approach, revealed by recurrent leakage, recurrent urinary tract infection or persistent or worsening of hydronephrosis, suggest the consideration of alternative treatment. Up to now, only surgery in the form of various types of bladder augmentation was proposed to achieve renal function preservation, low storage bladder pressure and continence.

24.4
Botulinum Toxin in the Treatment of Neurogenic Detrusor Overactivity

Approximately 10% of MMC patients are non-responders to anticholinergic medication or suffer side effects from anticholinergic drugs, even if administered intravesically [7]. There is increasing evidence that botulinum toxin (BTX) is a new, highly effective second-line treatment for MMC children with neurogenic detrusor overactivity (NDO).

The application of BTX in patients with NDO was pioneered by Schurch et al. [8]. Nineteen urodynamically proven NDO patients with spinal cord injury, who emptied their bladder with clean intermittent self-catheterization, were recruited; BTX-A (200 or 300 U; Botox, Allergan, Irvine, Calif.) were injected into the bladder, sparing the trigone, at 30 different sites, under cystoscopic guidance. After BTX-A injection, mean maximum bladder capacity increased by 62% ($p<0.05$) and mean maximal detrusor pressure decreased by 46% ($p<0.05$). In addition, 17 of 19 patients were completely continent at 6 weeks follow-up. The two patients who remained incontinent but still had moderate improvement in symptoms had received a lower dose of BTX-A (200 U). Ten patients reduced the anticholinergic medications required pre-injection, and the seven others no longer felt the need to take them at all. At 16 and 26 weeks after injection, 11 patients showed ongoing improvement in bladder function. Reitz et al. reported on a retrospective European multicentre experiment involving 200 patients with neurogenic bladder dysfunction treated by detrusor BTX-A injection [9]. Similar to Schurch et al.'s [8] previous findings, urodynamic testing revealed significant increases in maximum bladder capacity and decreases in voiding pressure at 3 months (200 of 200 patients) and 9 months (99 of 200 patients) follow-up. Lately, in a randomized placebo-controlled study, conducted in 59 patients with NDO, BTX-A injection significantly improved maximum bladder capacity and decreased number of incontinence episode per day during the 24-week study period [10]; thus, efficacy of detrusor injection of BTX-A to treat NDO reached a level 1 of evidence.

After an initial case report by Mall et al., only three prospective studies leading to four publications in the international literature have evaluated the efficacy of BTX-A injection in a paediatric neurogenic population suffering NDO [11]. Schulte-Baukloh et al. injected 20 children with NDO and MMC with 12 U/kg (maximum 300 U Botox, Allergan, Irvine, Calif.) [12, 13]. Urodynamic follow-up at 2–4 weeks after treatment revealed significant increases in mean maximal bladder capacity (35% increment) and significant decreases in maximal detrusor pressure (41% decline); however, while significant augmentation of maximum bladder capacity was demonstrated up to 6 months after treatment, no significant difference in maximum detrusor pressure was seen at 3–6 months follow-up. A more recent paediatric investigation with longer follow-up in 15 patients (mean age 5.8 years) supports previous studies by demonstrating an 118% increment of maximal bladder capacity ($p<0.001$) and a 46% decline of mean maximal detrusor pressure ($p<0.001$) with BTX-A injection [14]. Moreover, the clinical effects of BTX-A lasted a mean of 10.5 months and was similar after repeated injection. None of these studies recorded side effects related to the toxin or to the injection procedure. Corcos et al. reported on repeated injections in a population of 20 MMC patients (average age 13 years) [15]. They showed after the first injection that maximal bladder capacity increased from 197.7 to 285.3 ml ($p<0.01$), maximum detrusor pressure decreased from 44.7 to 29.9 cmH_2O ($p<0.01$), and compliance rose from 4.95 to 12.75 ml/cmH_2O ($p<0.01$). After the second and subsequent treatments (up to four), a similar range of improvement was observed for these three parameters.

24.5
Mechanism of Action

Botulinum toxin is the strongest naturally occurring lethal toxin known. It is produced by the anaerobic, rod-shaped, gram-positive bacteria *Clostridium botulinum*. Botulinum toxin binds rapidly and tightly to intramuscular nerve terminals, causing a prolonged local effect when injected directly into a muscle [16]. It evokes a degree of flaccid paralysis in skeletal muscles blocking presynaptic acetylcholine release by modulating a membrane-bound protein (SNAP-25). In smooth muscles it has been shown to trigger the release of nitric oxide that diffuses out of endothelial cells into smooth muscles producing relaxation [17]. In addition, Smith et al. have reported the effects of BTX-A on acetylcholine and norepinephrine release from the bladder and urethra [18], respectively. From their work, the authors concluded that the clinical manifestations of BTX probably vary, depending on the anatomical site of injection in the lower urinary tract and the frequency of nerve activity. Studies on guinea pig and rat bladder strips have revealed that BTX is able to impair both acetylcholine and ATP release from the urothelium [19, 20], suggesting that its extended use for treating patients with IDO is well justified.

There is new and increasing evidence that BTX has an antinociceptive effect separate from its neuromuscular action [21]. In the bladder, BTX-A, presumably by blocking neurotransmitter release from peripheral afferent nerve terminals, has been demonstrated to inhibit efferent nerve-mediated bladder contractions [20]. Lately, BTX-A injections have been shown to induce a dramatic decrease in bladder afferent neurons markers within the sub-urothelium of responder patients: the vanilloid and purinergic receptors TRPV1 and $P2X_3$ [22]. These findings support the role of the afferent nerve pathways in NDO and increase attractiveness of a treatment option able to block a plethora of neurotransmitters released from not only efferent, but also afferent, nerve terminals within the bladder.

24.6
Conclusion

General contraindications for BTX-A are myasthenia gravis, intake of aminoglycosides or any drugs that may interfere with neuromuscular transmission, Eaton-Lambert syndrome, breastfeeding, pregnancy, haemophilia, hereditary clotting factor deficiencies or other disorders that may cause bleeding diathesis.

Possible side effects of BTX-A injections are general weakness, dysphagia, diplopia and blurred vision. Adverse events related to BTX-A injections are rare in most published studies on NDO and absent of on paediatric population. Recently, DeLaet et al. [23] found in the literature a total of seven cases of transient generalized muscle weakness related to detrusor injection of BTX-A. Two cases were related to injection of 300 U of Botox, and five cases to injections of 1000 U of Dysport (Speywood Pharmaceuticals Limited, Berkshire, UK). All cases were reversible in 2 weeks to 2 months, and none of them required hospitalisation. It is noteworthy that experience with Dysport to treat NDO or IDO has at the time of this review not been published. The dosage conversion undertaken by Wyndaele and Van Dromme is based on the published Dysport/Botox (3:5) ratio [24]; however, in contrast to what has been reported for striated muscles, nothing is known about diffusion of the toxin in smooth muscles [25].

Higher diffusability of the English toxin (Dysport) might explain the observed generalized weakness. It is also surprising that in both cases bladder spasticity resumed after 2 months. A wrong injection technique or too high dilution volume might explain systemic diffusion of the toxin with consecutive generalized side effects in both cases. Additional data are required to assess the longevity of BTX and to optimize the dosage and timing of subsequent injections, when clinically indicated. Jankovic and Schwartz [26], who treated patients with blepharospasm and cervical dystonia, found an increase in the duration of benefit and a reduction in the number of complications during repeated injections, despite using the same dose of the toxin. Recently, Grosse et al. reported on the outcome of repeated injections (two to seven) of BTX-A toxin in 66 adults patients with NDO [27]. The time interval between subsequent injections did not change significantly (on average 9–11 months).

Clinical and urodynamic improvements were seen on all follow-ups. No increase in drug tolerance after multiple treatments was observed. At least no change in detrusor compliance was apparent, which clinically excluded any fibrosis of the detrusor after repeated injections. Haferkamp et al. did not find any change in the ultrastructure of the detrusor after BTX-A injection. Interestingly [28], contrary to reports on striated muscles, axonal sprouting within the detrusor was very limited after BTX-A injections, indicating pathophysiologically different reactions to the toxin between striated and smooth muscles.

Thus far, BTX-A injections to treat NDO in adults and children have very good documented success at short to medium term (up to four injections/re-injections in children). Since there is a need for re-injections, theoretically life long, long-term evaluation of efficacy, acceptance and cost is mandatory in order to define the actual place of detrusor BTX-A injections in the therapeutic algorithm of MMC patients. To date, it is a safe, reversible and mini-invasive alternative between failure of anticholinergics and bladder augmentation. Clarification is also required on the optimal dose and volume of BTX-A to inject into the bladder as well as the number of injection sites. This may be an explanation for the variability in some authors' results in terms of efficiency and longevity of treatment. Studies assessing health-related quality of life in children with NDO treated with BTX are needed, as this measure is of the greatest clinical significance to both children and their families.

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Endoscopic Approach to Urinary Incontinence in Pediatric Neurogenic Bladder Dysfunction

25

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25.1
Introduction

25.1.1
The Place of Urinary Incontinence in Pediatric Neurogenic Bladder

Urinary continence is still a difficult goal to achieve in neurogenic bladder patients. In pediatric age, urinary incontinence is mostly caused by congenital abnormalities, whereas the acquired causes are less frequent. Congenital anatomical defects are common in pediatric patients, such as exstrophy–epispadias complex, extravesical ectopic ureter in females, and urethral duplication.

Functional disorders of the lower urinary tract are frequently responsible of incontinence. Neurogenic bladder is usually the consequence of spina bifida (meningomyelocele), sacral agenesis, and other congenital abnormalities of the spina. Less frequently in children, neurogenic bladder can be the consequence of acquired lesions, such as spinal trauma and myelitis [1–4].

Classically, the functional classification of urinary incontinence has two mains groups of pathogenetic mechanisms: the failure of storage and the failure to empty [2]. The storage activity of the lower urinary tract can be failed as consequence of increased detrusor contractility or decreased outlet resistance (Table 1). The failure to empty the urinary reservoir is a possible consequence of decreased detrusor musculature contractility or increased outlet resistance (Table 1). In pediatric age, the congenital causes are more frequent and may be neurogenic, as in the neuropatic bladder due to of spinal dysraphism or sacral agenesis, or congenital anatomical defects (epispadias–exstrophy complex, urogenital sinus, etc).

25.1.2
Pharmacological and Surgical Treatment of Urinary Incontinence in Pediatric Age: a Perspective

The treatment of urinary incontinence in children is one of the most challenging tasks in our pediatric urological practice and several therapeutic tools may be adopted.

Pharmacological manipulation of the lower urinary tract is often useful in urinary incontinence treatment. Anticholinergic drugs may be used to decrease the detrusor overactivity and increase the functional capacity of the bladder [5]. Bladder outlet resistance can be reduced or increased by different drugs acting on the alpha-adrenergic receptors present on the trigone and cervico-urethral segment of the lower urinary tract [6]. Moreover, the pharmacological treatment for incontinence can be addressed to the renal urine production, modulating the tubular activity during night-time, as we can do in selected patients, to achieve nocturnal continence [7].

In the severe degrees of incontinence, surgery is needed to achieve adequate urine storage and output functions, to guarantee renal parenchyma safety and voluntary urinary control. A number of surgical procedures have been proposed, adopted, and rejected in the past century [8]. Some of them are mostly indicated for neurogenic incontinence and some are part of the staged reconstruction of the abnormally developed urinary tract

Table 1. Functional classification of urinary incontinence. (Modified from Berrett and Wein [2])

A. Failure of storage
  1. Increased bladder contractility
    a. Hypertonicity
    b. Neuropathic dysfunction
    c. Increased outflow resistance
    d. Infectious or inflammatory
    e. Idiopathic
  2. Decreased outlet resistance
    a. Congenital: stress
    b. Acquired: trauma or iatrogenic

B. Failure to empty
  1. Decreased bladder contractility
    a. Neurogenic dysfunction
  2. Increased outlet resistance
    a. Anatomic
    b. Functional (dyssynergia)

C. Congenital anatomic defects (accessory urethra, epispadias, exstrophy, ectopic ureter)

D. Psychogenic incontinence

E. Enuresis

[9–14]; however, the surgical procedures are often not fully adequate, and some degrees of urinary incontinence may result. Endoscopic treatment, using different implantable materials at the bladder neck or posterior urethra to increase the outlet resistance of the urinary reservoir, has been recently proven as effective for continence achievement. The endoscopic injection of these materials can be used as primary procedure in not severe cases of urinary incontinence, or as additional treatment for residual urine loss after any incompletely successful surgery [15, 16].

25.1.3
History

The use of injectable bulging substances for incontinence control is not new, as it was proposed more than three decades ago, although it still has not gotten full consensus and diffusion.

Endoscopic treatment of urinary incontinence was firstly proposed by Politano et al. in 1974, for adult female stress incontinence [17]. The authors used Polytef past (Teflon) as injected material, from the previous otorhinolaryngoscopic use on the vocal cords.

In pediatric practice, Polytef paste was used widely in the management of vesico-ureteral reflux since 1986 [18–20]. Endoscopic treatment was demonstrated to be effective in the neuropathic bladder of pediatric age patients [21], as well as in partial incontinence often persisting in the surgically corrected bladder exstrophy and epispadias patients [22]. In recent years, different materials have been proposed for endoscopic use and the basic research is still in progess [23], looking for the ideal substance.

25.2
The Clinical Approach

25.2.1
Indications for Endoscopic Treatment

The main indication for endoscopic injection of implantable materials to correct urinary incontinence in children is the failure of adequate urinary storage from decreased bladder outlet resistance. The urodynamic pattern encountered in these cases is intrinsic deficiency of the bladder neck and urethral sphincter, as we typically observe in adulthood stress incontinence [24]. In children, decreased outlet resistance from neurogenic dysfunction may be congenital or acquired.

It is necessary to point out that endoscopic treatment for incontinence in pediatric patients is not a full substitute for open surgery, but rather it is a complementary procedure. In fact, the endoscopic procedures with injections of bulging substances are able to augment any existing bladder outlet resistance, but cannot provide adequate resistance if there is none [22].

In the pediatric age group, the most commonly encountered conditions are the neurogenic dysfunctions and the structural deficiency of the bladder neck and sphinteric urethra in both sexes. In neurogenic incontinence, endoscopic injection is indicated as a primary procedure in children with a moderately low leak-point pressure. Other urodynamic parameters to be considered are the bladder capacity and compliance and the presence of detrusor hyperreflexia. In the latter case, endoscopic injection may be indicated if bladder hyperreflexia and hypertonicity are pharmacologically controlled. In other instances, the endoscopic procedure may be performed after previous surgery (bladder augmentation, detrusorectomy, bladder neck plasty), if it has failed to achieve complete continence [24].

25.2.2
Patient Selection

Careful selection of the patient, as candidate to endoscopic treatment to achieve urinary continence, is of central importance, before any attempt to perform the procedure. Urological evaluation of the upper and lower urinary tract is necessary to carry out in advance. Renal ultrasonography and nuclear scans are used for the evaluation of the upper tract. Cysto-urethrogram, endoscopy, and urodynamic studies using electromyography (EMG) of the urethral sphincter are also necessary for the lower tract evaluation. Moreover, a psychological evaluation of the child and his or her family is mandatory to access the patient's motivation and compliance.

Upper tract studies must rule out renal functional impairment: patients with chronic renal failure should be excluded from endoscopic treatment, to avoid the risk of glomerular filtration jeopardizing. Also, the polyuria of the patients in chronic renal failure can increase the imbalance between urine output and bladder functional capacity [24].

The urological evaluation of the lower urinary tract includes both imaging and endoscopic studies, as well as careful urodynamic evaluation to assess bladder capacity and compliance. EMG of the external urethral sphincter is necessary to verify the presence of detrusor–sphincter dyssynergia.

Any cervico-urethral obstruction must be excluded. Vesico-urethral reflux is not a contraindication to endoscopic treatment for incontinence, provided that the bladder reservoir is periodically emptied at low pressures, even with the use of intermittent catheterization. Reflux may be treated endoscopically at the same time incontinence, by subureteral injection of the some material [21].

The ideal functional characteristic for endoscopic treatment of neurogenic urinary incontinence are summarized in Table 2. The selection of patients is very important and other factors must be considered to achieve good results (Table 3). Patients must be motivated and adequately informed on the expected results, the need of a long-term follow-up and the possible need to repeat the procedure, if necessary.

Table 2 . The ideal lower urinary tract for endoscopic treatment

- Adequate posterior urethra and bladder neck
  a. As primary status
  b. After surgical reconstruction
- Easily catheterizable urethra for any clean intermittent catheterization
- Adequate functional bladder capacity correlated to age and 24-h diuresis
- Avoid detrusor hyperreflexia and poor bladder compliance

Table 3. Patient's inclusion criteria for endoscopic treatment of incontinence

Age >5 years
Partial sphincter deficiency
Adequate bladder capacity and compliance
Absent (or pharmacologically controlled detrusor overactivity
Child and parental motivation
Specific informed consent
Acceptance of possible repeated treatment
Long-term urological follow-up

25.3
The Injectable Materials

Several injectable substances, synthetic or natural alloplastic, have been proposed and often abandoned over the past two decades. Paraffin, vegetable oil, lanolin, silicon fluid, polytetrafluoroethylene (Polytef) particles, and bovine collagen are not used anymore for different reasons: risk of immunogenic response; potential long-distance migration; poor bulking property; excessive reabsorption; etc [23, 24]. Other materials, such as polydimethylsiloxane (Macroplastique, Uroplasty Ltd, Reading, UK) are still used, whereas alloplastic materials, grown in culture, such as chondrocytes and myocites, have been tested in terms of efficacy and safety experimentally, but have not been introduced into clinical practice [25].

Dextranomer particles suspended in 1% sodium hyaluronan (Deflux, Q-Med AB, Uppsala, Sweden) have been proposed as synthetic biomaterial and extensively used in Europe for the treatment of vesico-ureteral reflux [26, 27]. More recently, Dextranomer use has been successfully transferred to urinary incontinence treatment [28].

The ideal biomateial should be easy to inject and stable at the site of implantation. It should be inert, not immunogenic, well tolerated by the patient, and free of any mutagenic or carcinogenic potential. It should be, finally, cost-effective.

25.4
The Endoscopic Procedure

25.4.1
The Patient Preparation

Appropriate pre-operative urological work-up is necessary in advance. The procedure is usually performed under general anesthesia in children, as a day case. The patients preparing to receive a collagen implant should be skin tested for possible hypersensitivity to gluteraldehyde cross-linked bovine collagen. No special preparation or skin test are required for Deflux or Macroplastique implants.

25.4.2
Informed Consent

Endoscopic treatment for incontinence in children requires specific informed consent, with full disclosure to the parents about the efficacy of the procedure, the possibility of repeated procedures and the risk of adverse reactions or urinary outflow obstruction, even if almost rare. Opinions should be given also on current open-surgery techniques and its expected results, with the specific risks or possible complications.

25.4.3
The Different Techniques

Two main modalities to inject the chosen substance can be adopted: the transurethral or the peri-urethral injection. The transurethral technique is performed endoscopically using specific operative cystoscopes (Fig. 1) [16]. A special needle is introduced through the operating channel of the cysto-urethroscope and the mucosa of the bladder neck is transfixed for 2–3 mm (Fig. 2). The material is injected usually at the 5, 7, and 12 o'clock positions in males (Fig. 3). The six o'clock site is spared in boys, to prevent injury to the prostatic tissue. In girls, the injection is carried out at the 3, 6, 9, and 12 o'clock positions (Fig. 4).

A new device has recently been developed to obtain four symmetrical sites of injection through a specific implacer, without the need of endoscopy. The device, named Zuidex (Q-Med, Uppsala, Sweden), can be used in female patients older than 7 years of age (Fig. 5).

The peri-urethral technique is performed starting with the endoscopic check of the urethra and bladder neck. Then, the needle is inserted percutaneously through the perineum, approaching the mucosa of the urethra from the outside. The urethroscopy is mandatory for controlling the correct position of the needle during the injection and for avoiding the risk of spillage inside the urinary lumen or, conversely, the too deep positioning of the needle tip, outside the urethral and bladder neck wall.

In both the approaches, the positioning of a transient (48–72 h) suprapubic catheter is strongly suggested to avoid the risk of urinary outflow obstruction and to check any urine residual, after the submucosal injection of bulging substances on the bladder neck. The use of an indwelling transurethral catheter should be avoided, as it could cause dislodgment of the implant in the first few hours. Most patients, however, are able to void with mild straining and urinary retention is seldom observed after submucosal injection of material for continence. In children undergoing intermittent catheterization, it can be resumed safely after 3–4 days. In these cases, percutaneous suprapubic cystostomy is mandatory until intermit-

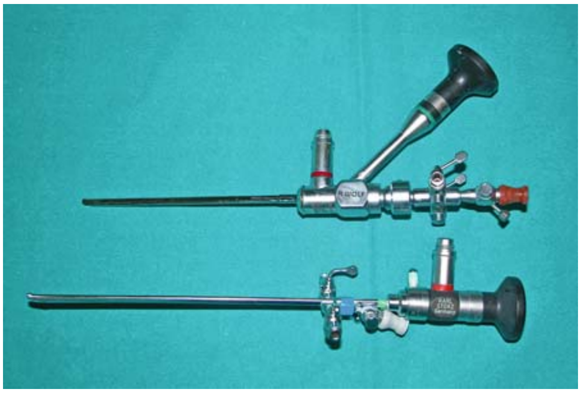

Fig. 1. Pediatric operative cystoscopes, caliber 10 Ch, provided with straight and angulated operative channel (5 Ch)

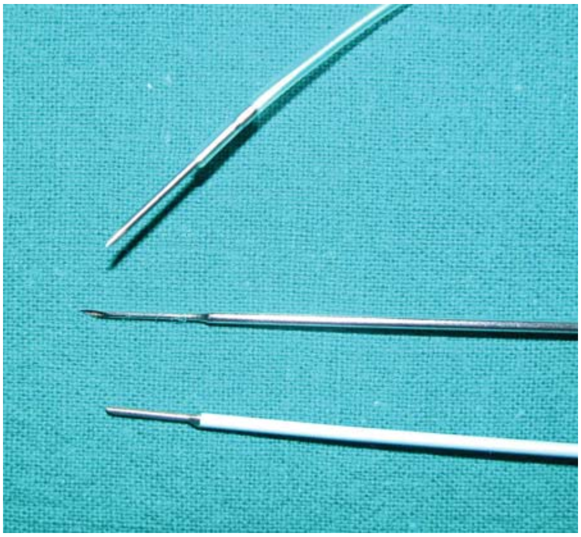

Fig. 2. Different needles and cannulas (flexible and rigid), necessary to perform endoscopic injection of bulging materials. The metallic rigid cannula is preferred.

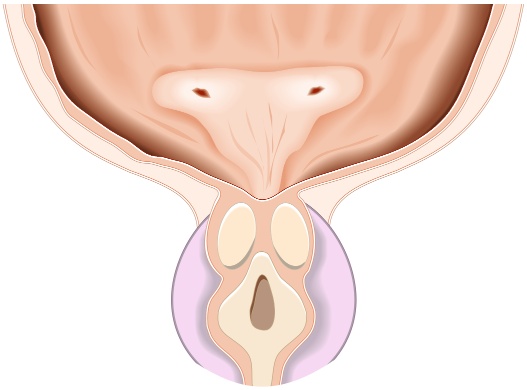

Fig. 3. The correct implant site of the material (Deflux, Macroplastique, or other) in the male patient: at the bladder neck, proximally to the *veru montanum*

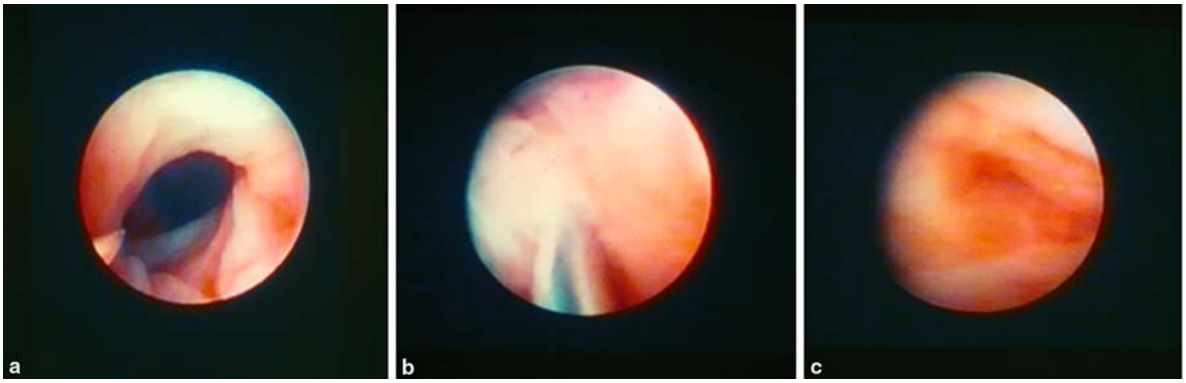

Fig. 4. **a–c** Endoscopic view of a wide and soft bladder neck, without scarred tissue, in a female neurogenic bladder, before Dextranomer injection for continence. The needle at 6 h positioning during the injection. The "visual occlusion" of the urethral lumen has been achieved.

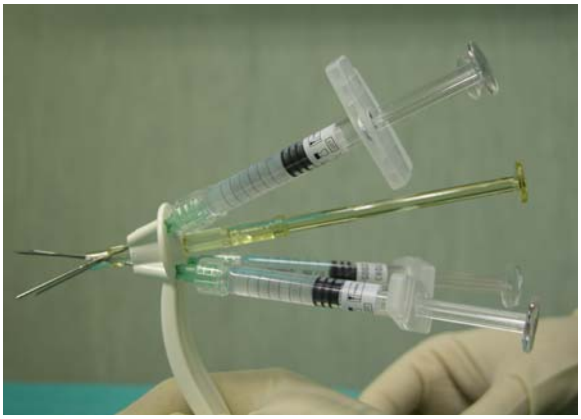

Fig. 5. The Zuidex implacer

tent catheterism is fully re-established [29]. Antimicrobical prophylaxis is administered until the suprapubic tube is maintained and anticholinergic drugs are continued longer, if detrusor overactivity or hypertonicity were previously demonstrated [4, 5].

25.5
The Results of Endoscopic Approach to Urinary Incontinence

Results of submucosal pericervical injection of bulging material for urinary Incontinence varies significantly, the outcome depending mostly on the underlying disease responsible for incontinence and from the degree of the structural and functional abnormality of the bladder outlet tract. Correct anatomical and urodynamic conditions are the predicting factors of favorable outcome. The most important factors influencing the results of endoscopic treatment are adequate capacity, good compliance, absence or pharmacologically controlled detrusor overactivity and somewhat persisting outlet resistance, and absent scar tissue on bladder neck. So, in neurogenic urinary incontinence, results are often better than in the exstrophy–epispadias complex surgically treated cases.

Results of endoscopic treatment for urinary incontinence are basically judged as daytime dry intervals between bladder emptying and as functional bladder capacity. Our experience until the year 2000 is given in Table 4. The pad test is useful for detecting dryness achievement during daytime and night-time. In the 122 endoscopic treatments performed in children from 1988 until 2000 [29], we observed that 20% of patients became fully dry and more than 50% gained significant dryness improvement during daytime. Functional bladder capacity increased from 85 to 125 ml. Overnight dryness achievement was less encouraging, as only about 12% of patients become fully dry at night and less than 40% improved the nocturnal pad test or experienced nocturia [30]. The use of desmopressin before sleeping has been demonstrated to improve the nocturnal results [7].

25.5.1
Technical Failures

One of the most frequent pitfalls of the endoscopic treatment is the leakage of the material into the urethra or bladder neck during the injection. The difficulty at the injection time can lead to immediate failure of the procedure as a consequence of spillage of the material, usually due to the presence of scar tissue on the posterior urethra and bladder neck, commonly from previous surgeries. In such cases, the endoscopic procedure should be aborted [30].

Table 4. Endoscopic treatment for urinary incontinence: overall experience at the "Bambino Gesu" Children's Hospital. (From [29])

Material	Period of treatment	No. of patients	No. of treatments
Bovine collagen[a]	1988–1998	37	69
Macroplastique[a]	1998–2000	9	16
Deflux	1998–2000	16	37
Total	1988–2000	62	122

[a] Data presented at European Society for Pediatric Urology Annual Meeting Pre-Congress Symposium, Aarhus Denmark, 2001

Two different reasons for late failures of the submucosal injection on bladder neck are observed:

1. Partial reabsorption with volume loss of the implanted material
2. Dislodgment of the bulking substance from the site of implant

Usually, results become stabilized after 3 months from the procedure and the obtained improvement stay constant along the years; however, the long-term outcome may be influenced by functional changes in the bladder activity (as a newly developed overactivity) or by variations on the pelvic statics, especially in women who strain to void [29].

25.6
Conclusion

Submucosal pericervical injection of implantable materials for urinary incontinence in childhood and adolescence is resulted as an effective and minimally invasive method (day-case procedure), with very favorable cost/result ratio and high patient preference, if we can guarantee (a) the rigorous patient's selection; and (b) the precise endoscopic injection technique.

The role of pharmacological urotherapy, uro-rehabilitation, endoscopic treatment, and open surgery needs to be utilized in an individualized and integrated manner, as the functional and anatomical situations could be very different in the neurogenic pediatric population. Anyway, we must consider that urinary continence achievement is a basic need in the pediatric and adolescent population, one that we should obtain at all costs.

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Sling Procedures for Neuropathic Sphincter Incontinence

26

Tom P.V.M. de Jong

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26.1
Introduction

Approximately 50% of patients with spina bifida suffer sphincter incompetence based on the neuropathic lesion [1]. In caudal regression syndrome, with or without anorectal malformation, half of the children have neurogenic lower urinary tract dysfunction and 70% of those hyporeflexia of the sphincter. Also, tethered spinal cord, spinal trauma, and surgery for anorectal malformations can produce motor neuron problems of the pelvic floor with, as a consequence, urinary incontinence [2–4].

To become continent, these children need surgery to enhance bladder outlet resistance. Many procedures are used worldwide. Flap-valve procedures (Kropp, Pippi Sale), formal bladder neck reconstruction, and AMS sphincter prosthesis have their pros and cons. Theoretically, with an AMS sphincter, the patient could be able to void naturally. In practice, most patients with sphincter prosthesis still have to rely on clean intermittent catheterization (CIC). In those cases, the sphincter prosthesis acts like an expensive sling. Because of this, in the past, we have opted for the external abdominis fascial sling as a primary solution for sphincter incontinence in spina bifida patients [5–12].

Demands for quality of enhancement of urethral resistance are much higher in neuropathic sphincter incompetence than in regular stress incontinence because of the absence of the guarding reflex in spina bifida patients. The guarding reflex (S2–S3) is the twitch of the puborectalis muscle in response to high abdominal pressures. It can be measured by rectal exam, by pelvic floor EMG recording, or by perineal ultrasound when the patient is asked to cough.

This absence of the guarding reflex is thought to be the main reason that standard procedures for stress incontinence in female patients have insufficient results in spina bifida patients, although a recent publication on the use of TVT in female neuropathic sphincter incontinence claims 10 of 12 dry patients [13]. In our hands and in the literature, results of standard colposuspension operations have been disappointing [12, 14, 15].

26.2
Pre-operative Assessment of Bladder Function Before Bladder Neck Procedures

The cornerstone of modern urologic treatment of spina bifida patients is preservation of normal kidney function. To avoid unpleasant surprises regarding bladder and kidney function, after bladder neck surgery meticulous urodynamic assessment of the bladder is needed before surgery. Clinically, sphincter-incontinent patients have an empty bladder most of the time due to urinary leakage with low pressures. Until the time of bladder neck surgery, it can be stated generally that hardly any risk exists for the kidneys in children with a paralytic sphincter. Before surgery, it is imperative to have information as to whether the bladder has an adequate capacity, a safe compliance, and absence of detrusor overactivity with or without antimuscarinic therapy. A baseline urodynamic study (UDS) is needed to obtain this information. When leakage during UDS is too much to obtain adequate filling of the bladder, the UDS must be repeated in the same session with balloon-catheter occlusion of the bladder neck. When detrusor overactivity occurs, capacity is low for age, or the compliance is unsafe for the upper tracts, a second UDS is needed after 6 weeks of antimuscarinic therapy. Bladder neck surgery can be planned when the bladder parameters are safe. If not, enhancement of bladder quality must be planned beforehand by combining the bladder neck procedure with a detrusorectomy of the bladder or an ileocystoplasty. For capacity, we use the formula (30+30 × age) = capacity for age (in milliters). At least 70% of capacity for age is needed before incontinence surgery without bladder augmentation. We consider compliance safe when pressures are below 20 cm H2O up to 70% of capacity for age. Detrusor overactivity must be absent when the patient is on antimuscarinic therapy.

26.3
Patient Preparation

In our hospital, all spina bifida patients are on CIC and antimuscarinics from birth onward. Patients with an overactive sphincter use CIC five times daily, together with antimuscarinics, and are dry on this regime. Patients with an underactive sphincter use CIC twice a day to maintain the habit and to ensure complete emptying of the bladder twice a day to prevent urinary tract infections (UTIs). Parents and children are informed that after bladder neck surgery CIC is imperative five times a day for the rest of their life. When a child is not yet on CIC this is learned firstly. Surgery is planned only when the patients and/or parents are fully compliant with the CIC regime. When the patient's bladder needs to be treated pharmacologically with antimuscarinics, they also have to accept that this will be needed for the rest of their life. To prevent side effects, antimuscarinics can be given intravesically bid in most cases.

26.4
Timing of Surgery

There is no age limit for bladder neck surgery. In the past it was feared that prepubertal sling suspensions would cause problems during puberty because of lack of growth of the sling. Apparently, both in boys and in girls some growth of the sling occurs during puberty. No prostatic problems, or problems caused by extreme suspension with a short sling, have occurred in any of the patients that have gone through puberty. Also, urinary continence is preserved through puberty in the approximately 25 patients who had sling surgery at a younger age and have passed through puberty. We offer urinary continence by surgery routinely at school age, i.e., 5 or 6 years. Sling surgery can be performed as early as a few months of age. In a few cases that had a strict medical indication for bladder surgery during infancy, ureteral reimplant surgery was combined with sling suspension without any side effects.

26.5
Other Surgery Combined with Sling Suspensions

Many indications have been raised over time to combine sling surgery with the construction of a catherizable stoma in the umbilicus or the lower abdomen; firstly, the patient's own preference to avoid transfers out of the wheelchair for each catheterization. This applies predominantly to wheelchair-bound girls. For them, a stoma also obviates the need for a special toilet for physically challenged people for each catheterization, thus increasing their independence. Secondly, parental preference takes a role when the need for transfers for CIC causes health problems for the caretakers. A 4-year-old spina bifida patient can be a heavy load for a mother with back problems. Thirdly, parental preference comes into play again for reasons of privacy for their school-going child. A stoma prevents the need to expose the genitalia of their child to every caretaker doing CIC at an institution.

Sling surgery can be combined routinely, when indicated, with other bladder surgery such as ileocystoplasty, detrusorectomy, and ureteral reimplantation.

26.6
Sling Type and Sling Harvesting

Results of artificial slings in myelomeningocele have been disappointing, due mainly to erosion of slings, which need removal with subsequent urinary leakage. One report on the use of TVT claims success in treating female neuropathic incontinence, but simple colposuspension for female sphincter incontinence has proved to be insufficient in most cases. The TVT insertion is supposed to be a substitute for colposuspension and thus may be regarded as an insufficient surgical solution for sphincter incontinence. Moreover, in pediatric urologic cases, surgery by vaginal approach is not possible. External fascia abdominis strips have been used as slings predominantly. They can be used as a free transplant or can be used unilaterally fixed to the pubic bone. In virginal cases, the externus abdominis fascia is opened longitudinally in the midline and the sling is made of a 2-cm-wide strip of fascia running from the umbilicus to the pubic bone. After previous surgery by transverse lower abdominal incision, the sling can be made from a 2-cm-wide strip of fascia running from the pubic bone to the spina iliaca anterior superior. In case of multiple previous abdominal operations, a free graft of tensor fascia lata can be harvested and used as a sling. We prefer to reserve this procedure for post-pubertal patients, for fear of lack of growth potential of the sling through puberty.

26.7
Sling Surgery in Girls

Sling suspension of the bladder neck in female patients averages good results concerning urinary continence. Several ways exist to find the way around the bladder neck in girls. The standard well-known technique is to identify the level of the bladder neck by feeling the balloon of a transurethral Foley catheter, and to access the plane between the bladder neck and the anterior vaginal wall from above. This procedure can be very difficult in girls with severe spinal deformities. A certain risk to enter the urethra or the bladder neck when searching is always present, also in patients with normal anatomy. To avoid this risk, in post-pubertal female patients, many choose the possibility to incise the vaginal wall at the level of the bladder neck, and to bring the sling around under direct visual control. First in prepubertal girls, and later in all cases, we adopted the habit of putting the sling through the vagina. This method has two advantages: (a) the risk of bladder neck lesions is eliminated; and (b) there is less chance for sling erosion. Sling-erosion risk is higher in spina bifida patients than in patients with stress incontinence, because the sling must be tightened more strongly in neuropathic sphincter incompetence.

A description of the procedure in 24 cases [12] is given: Patients are surgically treated under antibiotic prophylaxis with amoxicillin/clavulanic acid and gentamycin. Flushing the vagina with povidone/iodin 10% solution is done as vaginal toilet. Most patients are surgically treated through a transverse lower abdominal incision with longitudinal opening of the rectus abdominis fascia in the midline. Patients who have had an ileocystoplasty as well are surgically treated through a longitudinal lower abdominal midline incision. A 10- to 15-cm-long and 2-cm-wide paramedian strip of the rectus abdominis fascia is made, leaving the caudal end fixed to the pubic bone. In patients who have had a previous transverse incision of the rectus fascia, a 2-cm-wide strip of externus abdominis fascia is harvested, running from the pubic bone to the anterior superior iliac spine. The bladder neck and anterior vaginal wall are identified with a transurethral balloon catheter and freed, comparable to the preparation for a Burch-type colposuspension. A metal clamp is introduced into the vagina and used to lift the anterior vaginal wall left and right of the bladder neck. Using electrocautery, two small holes are made in the vagina and a vessel loop is passed around the bladder neck through the holes. Because the majority of patients are prepubertal, and no patient has given birth before the operation, there is not enough room in the vagina to attempt creating a submucosal tunnel in the anterior vaginal wall. The fascial sling is fixed to the vessel loop and passed through the holes. The sling is passed bluntly through the contralateral rectus abdominis muscle and overlying fascia and is tightly fixed to the tubercle of the pubic bone with strong polyglycolic acid sutures (Fig. 1). Tension on the sling before fixing is high leaving one finger between the symphysis and the bladder neck, in contrast to sling suspension for stress incontinence, where the sling is barely tied. In the majority of our patients the sling operation has been combined with other procedures: ileocystoplasty in 5; detrusorectomy in 13; continent catheterizable stoma in 8; and extravesical ureteral reimplant in 3. Patients were treated with low-pressure suction drainage before the bladder for 2–4 days. Bladder drainage is done by transurethral catheter for 7 days, combined with suprapubic catheter in cases of ileocystoplasty. Hospitalization for the patients without ileocystoplasty was 3 days. The patients who had no catheterizable stoma resumed CIC after 7 days. (Special attention is given to teach patients the changed direction of the urethra when transurethral CIC is resumed.)

Of our series of 24 patients, 22 became dry, 19 after the sling suspension and 3 patients after additional injection of bulking material on the sling. When, for some reason, colposcopy is performed a few months after sling suspension, the sling appears to be completely covered by vaginal mucosa and can no longer be identified.

26.8
Sling Surgery in Boys

Results of sling suspension of the bladder neck in boys with neuropathic sphincter incompetence vary in the

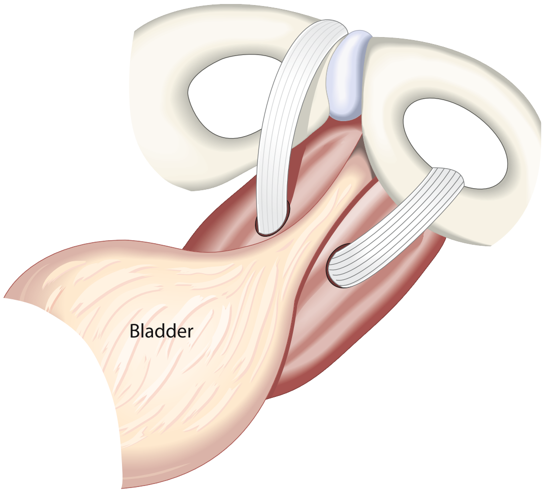

Fig. 1. Artist's impression of a transvaginal sling suspension in a female

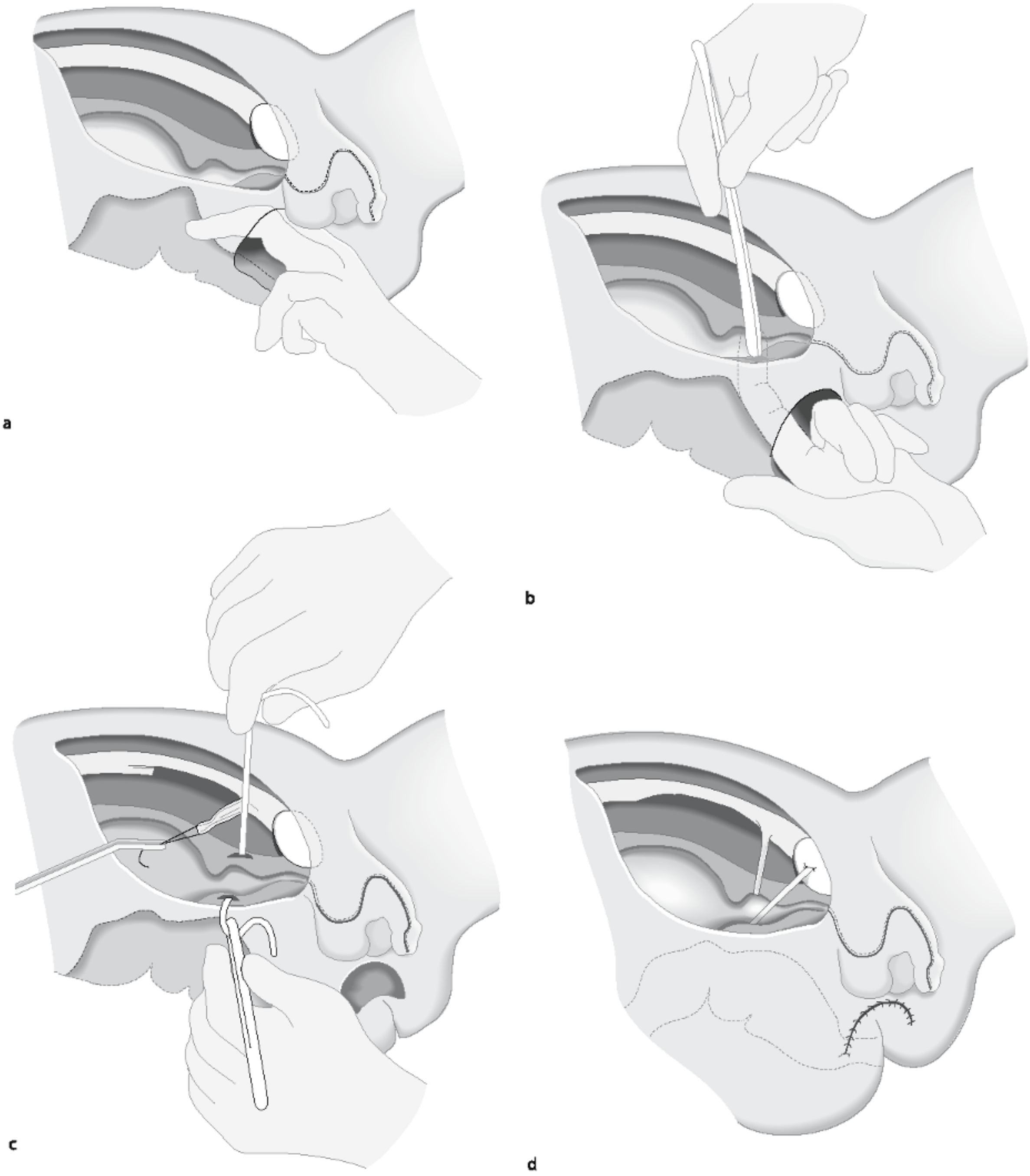

Fig. 2. The different steps to take in performing an abdominoperineal sling suspension in a boy

literature, more widely than in girls. To wrap the sling around the bladder neck, the plane between the bladder neck/prostate and the rectum must be accessed. Three possible techniques have specific advantages and disadvantages. Firstly, from the abdominal wound, the pelvic diaphragm can be opened, left and right, and a pathway can be dissected for the sling, bluntly, around the bladder neck. The disadvantage of this technique is the risk of passing into the prostatic urethra with the right angle that is used to feel around. Experienced urologic surgeons do not take this argument seriously, but the fact is, in practice, that most surgeons perform this operation relatively infrequently (just a few cases per year).

Secondly, the abdominoperineal approach is used to access the plane between the bladder neck and the urethra. With gauze in the rectum for better identification, an inverted "U" incision is made in the perineum. The centrum tendineum of the pelvic floor is opened in the midline, and by blunt dissection with a finger the plane between prostate and rectum is accessed with the transurethral balloon catheter as a landmark. Pulling the catheter and feeling the position of the balloon can help in identifying the level of the bladder neck. Midline connections between the prostate and the rectum are cut sharply. With the index finger following the rami of the pubic bone, the pelvic diaphragm is perforated bilaterally and a vessel loop is passed around the bladder neck from left to right. The sling can subsequently be pulled through and fixed to the contralateral pubic bone (Fig. 2). The most important advantage of this procedure is the short time (approximately 20 min) needed to develop the plane around the bladder neck, and the fact that the bladder does not need to be touched at all.

A third way to find the path around the bladder neck has recently been proposed by Lottmann et al. [16]. The complete bladder is dissected from the peritoneum and the rectum until it is fixed only by the urethra and both ureters with the vascular pillars. The sling can easily be passed around under direct visual control and exactly at the level of the bladder neck (Fig. 3).

It is difficult to determine which of the three approaches is the best; all three have enthusiastic followers. We have had two urethral defects by two experienced surgeons in a small series of the abdominal approach, going directly around the bladder neck. We have had one urethral defect leading to bladder neck closure in 50 abdominoperineal-operated patients. The present author's experience with the Lottmann et al. [16] approach is limited to three successful cases and, because of operative time and for fear of limited bladder vascularization, the abdominoperineal approach has been re-adopted.

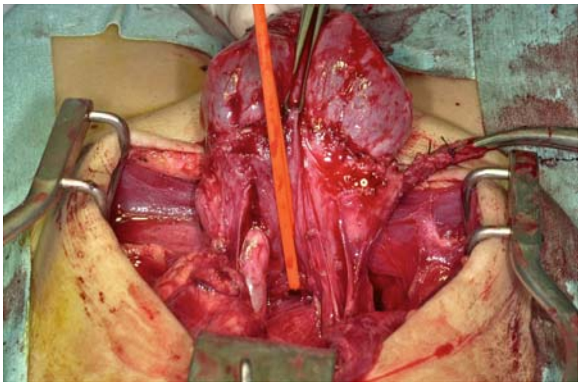

Fig. 3. A sling suspension after freeing the bladder completely. The left ureter has had an extravesical reimplant and a detrusorectomy was performed. The vessel loop is around the sling.

The amount of tension that needs to be put on the sling is an important issue. In the past, we tried to adjust tension by measuring urethral pressures and leak-point pressures during surgery, without significant outcome. Presently, we determine the tension on the sling by measuring the ability to pass a relatively large Foley catheter past the sling, e.g., a 12-F catheter in a 7-year-old boy.

In selected cases, in patients with anal atresia after prior rectal pull-through surgery, an abdominal approach might be considered necessary to pass around the bladder neck. In a series of 14 abdominoperineal-operated patients continence was achieved in 100%; 1 case needed subsequent injection of a bulking agent to achieve continence. It is significant that in that series erectile function of the penis proved to be preserved after sling suspension [11].

False routes after sling suspension are a risk. Of approximately 50 males, we have had to construct a catheterizable stoma in 5 patients, 4 because of a false route and 1 because of a huge congenital prostatic cyst.

26.9
Urinary Incontinence After Sling Suspension

Especially in females, patients need to be warned that urinary incontinence is not to be expected during the first months after surgery. This is possibly due to a temporary rigidity of the tissues shortly after surgery. When incontinence persists and UDS has excluded bladder behavior as the main reason, one can try, after approximately 6 months, to gain continence by injecting a bulking agent at the level of the sling. After sling suspension, bulking agents can be successful because the sling acts as a backing for the injected material. Results of injectional therapy are good in cases where the injected channel is not used for CIC, i.e., in patients with a catheterizable stoma. When the channel is used for CIC, results of bulking agent injection appear to be disappointing in the long term. In 5 of 100 cases we ended up doing a formal bladder neck reconstruction after failed sling suspensions. The other 95 cases were spared complicated intravesical procedures to achieve urinary continence.

26.10
Conclusion

Sling suspension of the bladder neck in neuropathic sphincter incontinence is a relatively easy and successful way to achieve urinary continence. It obviates the need for complicated intravesical procedures and can be combined with any other type of bladder surgery. In females, the transvaginal way is easy and success is nearly guaranteed.

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Bladder Neck Reconstructions in Children with Neurogenic Bladder

27

Antonio Savanelli · Ciro Esposito

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27.1
Introduction

Total urinary incontinence due to sphincter incompetence is a difficult problem, and exploring its correction is the purpose of this chapter. In 1922 Young reported the first successful correction of urinary incontinence by narrowing the urethral and bladder neck lumens [1]. In 1949 Dees modified the Young technique adding the concept of lengthening the urethral tube to that of narrowing, including bladder neck muscle up into the trigonal area [2]. In 1964 Leadbetter introduced an operation that involved tubularization of the trigone with cephalad reimplantation of the ureters by creating muscular flaps from the bladder neck and proximal urethra, which were used to wrap the newly created proximal tube [3].

Since that time many surgical procedures have been proposed, but not very good results have been reported. The surgical management of urinary incontinence in children with neurogenic bladder dysfunction remains challenging.

In 1973 the artificial urinary sphincter was proposed by Scott as surgical option for the neuropathic patients with low urethral resistance, allowing normal voiding without intermittent catheterization [4].

Urethral and colposuspension procedures performed from 1949 to 1990 determined good functional outcome, but long-term results are not satisfactory in girls with spina bifida [5].

In 1983 Jeffs et al. applied the Young-Dees-Leadbetter (YDL) bladderneck plasty to a staged repair of exstrophy by supporting a lengthened urethra by a suspension [6–8].

Mollard in 1980 modified the Young-Dees-Leadbetter bladder neckplasty performing an eccentric triangle mobilized and brought around the bladder neck after mucosal closure and ureteral reimplant [9].

In 1986 Kropp and Angwafo proposed a reconstructive procedure: an anterior bladder wall flap was tubularized and reimplanted into the posterior bladder wall. The procedure has been associated with catheterization difficulties and reduction of the bladder capacity [10].

In 1990 Koff utilized a wide anterior bladder flap to accentuate the muscular bladder neck [11].

In 1993 Mitchell et al. improved results using a modification of the Young-Dees-Leadbetter bladder neck repair in 31 patients with exstrophy and 14 with myelomeningocele [12, 13].

In 1994 Pippi Salle modified Kropp's technique to simplify the procedure and to improve the results, up to 70% of continence rates [14–16].

In 1997 Snodgrass reported another simplified Kropp bladder neck reconstruction to achieve urinary continence. With his technique he does not perform the separation of the bladder neck from the remainder of the bladder [17].

In the past years the urethral sling has became popular in the treatment of sphincter incompetence in female patients and has been used for neurogenic incontinence. McGuire reported 100% success among eight female patients with myelomeningocele, and Elder a 90% in 10 patients [18–20].

Colpo-wrap procedure (tightening of the bladder neck by mobilizing the anterior vaginal wall and wrapping it around the bladder neck and proximal urethra in the sense of a vaginoplication, has been reported with results comparable to those of the vaginal sling procedure [21].

Last, but not least, the endoscopic treatment allows to obtain good results above all in cases with a not very large bladder neck. Bulking agents may be a reasonable alternative to more invasive reconstructive procedures or can be utilized as additional treatment after a not completely successful surgery [22].

27.2
Indications for Treatment

The goals in patients with neuropathic bladder remain the preservation of normal kidney function, the protection from urinary infections, and finally, the urinary and bowel continence to guarantee a good quality of life.

The introduction of intermittent catheterization and pharmacological therapy has considerably reduced the incidence of damage to the kidney function and of the cases of urinary incontinence, but in most series incontinence remains variable from 12 to 76% [10, 23, 24].

Only after conservative therapy has failed must we consider patients for surgical intervention. In these cases a careful selection of the patients and an accurate preoperative study can suggest the right surgical strategy.

The patient must be motivated, intelligent, and endowed with a good manual skill to be able to practice intermittent catheterization.

Preoperative urodynamic tests to evaluate the bladder capacity and the compliance are necessary to establish the need of associating an augmentation cystoplasty with the bladder neck procedure, considering that a good urinary continence requires good bladder capacity.

The bladder capacity should be at least the calculated normal value for age to assure storage of an appropriate urine production during 3–4 h (age in years + 2) × 28 (in milliliters) according to Koff's rule [25]. If the capacity is <70% of the value expected according to the age, it is necessary to include a bladder augmentation.

The urodynamic tests have to study the detrusor activity also occluding the bladder neck for a more accurate evaluation of capacity, and to exclude the presence of an overactive detrusor.

In case of pain during catheterization, the patient may be reluctant to perform clean intermittent catheterization (CIC), and in these cases a cutaneous stoma must be performed.

Having recourse to a stoma must be considered the last possible solution after every attempt of reconstructing a physiological urinary tract has failed. The choice of the placement of the stoma on a child must take into consideration changes in body constitution and scoliosis may interfere with previous urinary reconstruction by obscuring the stoma or causing repeated bag dislodgement.

Before surgery, the endoscopic treatment is indicated as the primary procedure in non-severe cases of urinary incontinence.

27.3
Surgical Procedures

Bladder neck reconstruction should be undertaken in children, preferably not before the age of 4 years. No age-related contraindication exists, and the indication for surgery is decided in agreement with the child's parents.

The main procedures utilizes a flap valve or tunnel to achieve urethral closure. Augmentation cystoplasty and appendicovesicostomy can be simultaneous procedures with bladder neck reconstructions when they are indicated.

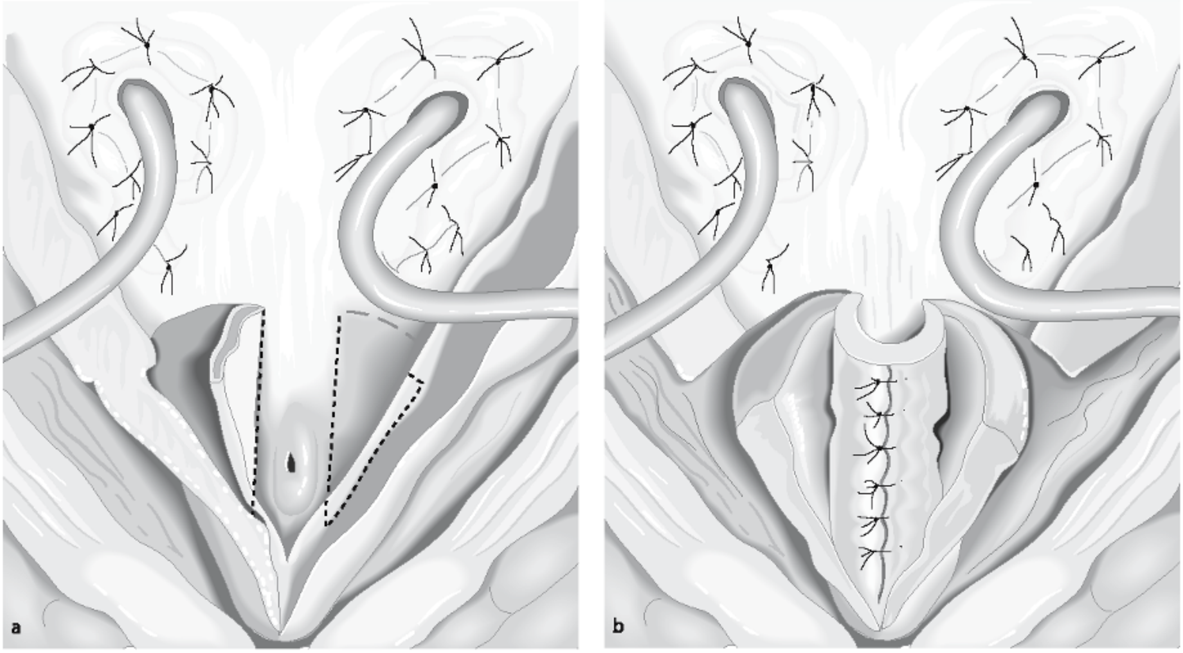
27.3.1
Young-Dees-Leadbetter Neck Repair

The procedure is undertaken through a broad Pfannestiel incision. The bladder is opened by a midline incision and a self-retraining retractor is inserted. A reimplantation at a higher level is desirable as a preliminary to bladder neck reconstruction. This reimplantation can be performed by Politano or Cohen technique.

A posterior midline mucosal strip is outlined by vertical incisions and two triangles of mucosa lateral to this strip are excised (Fig. 1A). The length of this strip should be at least 4 cm and the width 2–2.5 cm. The strip is then rolled into a tube over an 8-F silicon stent and incisions are made in the bladder muscle at the new bladder neck level, thus forming two muscular flaps (Fig. 1B). Then the two de-epithelialized muscular flaps are wrapped around the neo-urethra, one forming the inner layer and the second muscle flap overlaps the first and gives support to the new urethra and bladder neck (Fig. 1C). Omentum can be brought around in front of the new bladder neck. Finally, the bladder is closed with a suprapubic cystostomy drain and left in for 3–4 weeks.

Koff has modified the YDL by using a compressive cuff of bladder muscle. Unlike the YDL operation, the muscle is fashioned into a single, long, brad-based flap instead of two laterally based triangles (Fig. 2).

Mitchell improved results using modification of the Young-Dees-Leadbetter neck repair: a V flap of bladder neck is incised anteriorly leaving a strip of urethra and bladder neck posteriorly approximately 15 m wide; then the urethra, bladder neck, and trigone are tubularized while the anterior bladder is closed vertically. The point of the V flap ends at superior extent of the closure, avoiding the loss of bladder volume.



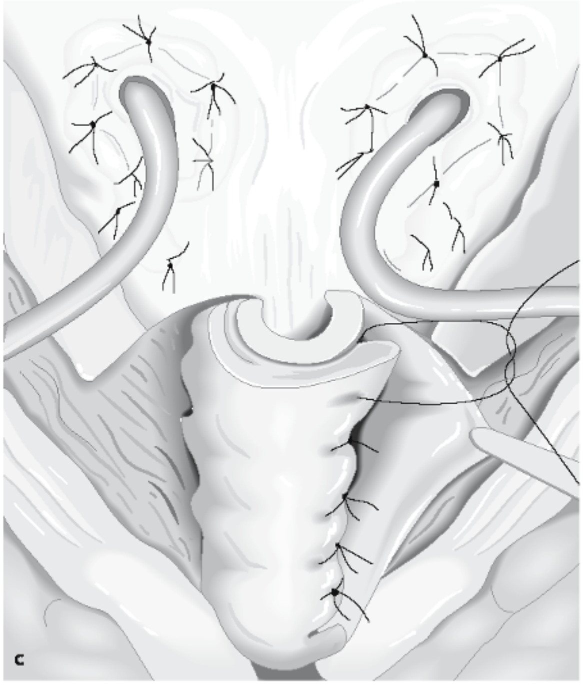


Fig. 1. **a** Young-Dees-Leadbetter procedure: A posterior midline mucosal strip is outlined by vertical incisions and two triangles of mucosa are excised. **b** A posterior midline mucosal strip is rolled into a tube over an 8 F catheter. A reimplantation at a higher level has been performed. **c** The two muscular flaps are wrapped around the neo-urethra.

27.3.2
Kropp Procedure

The anterior bladder wall, bladder neck, and proximal urethra are exposed.

A rectangular bladder pedicle flap, whose length and width equal the planned length and diameter of the new urethra (in millimeters), is outlined on the anterior bladder wall. The flap is based upon the bladder neck (Fig. 3A). The bladder is separated from the bladder neck and then the flap is rolled into a tube over an 8-F catheter and sutured. A submucosal tunnel is fashioned between the ureteral orifices and the urethral tube is pulled through the tunnel (Fig. 3B).The bladder finally is secured to the bladder neck with several stitches and the urethra is sutured to the bladder. The bladder is closed down to, and around, the bladder neck. Snodgrass, as first suggested by Belman and Kaplan, reported the operation from the original description by Kropp and Angwafo, modified in two aspects: (a) the bladder neck was not completely detached from the remainder of the bladder; and (b) the detrusor tube was laid into a groove on the bladder floor rather than tunneled submucosally [17, 26].

27.3.3
Salle Procedure

A Pfannestiel incision is performed or a midline incision if an enterocystoplasty is needed. A wide-based anterior bladder flap measuring at least 5 cm in length and 2.5 cm in width at the base, and 1.5 cm at the top, is performed

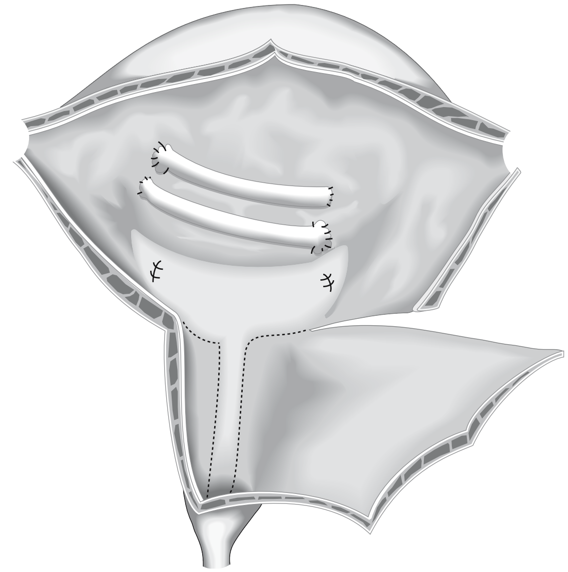


Fig. 2. Koff procedure: A posterior mucosal strip will become neourethra and demucosalized bladder muscle flap will wrapped around neo-urethra.

(Fig. 4a). The lateral mucosal edges of the anterior flap are excised to avoid an overlapping of the suture lines in the procedure (Fig. 4b). Two parallel incisions are made in the posterior bladder wall (Fig. 4c). If necessary, the ureters are transversely reimplanted in a more cephalad position. The posterior mucosa laterally on each side of the mucosal strip, 0.7 cm large, is mobilized from the detrusor. The anterior flap is anastomosed to the posterior bladder mucosal strip in an onlay fashion (Fig. 4d). The posterior lateral mucosal edges are approximated over the neo-urethra. Some authors have reported satisfactory results without mobilizing the posterior mucosa, leaving the bladder serosal surface of the flap exposed to the intravesical urethra. Finally, the edges of the bladder were sutured over the lengthened urethra, creating a flap valve without tension to avoid compression of its base and impairment of its vascular supply.

If some scars are present in the midline anterior bladder wall a lateralized flap can be created and sutured in an onlay fashion to the posterior bladder wall in two layers (mucosa–mucosal and muscle–muscular) [14–17, 27].

27.4 Discussion

The treatment of urinary incontinence secondary to diminished urethral resistance remains a difficult challenge with respect to the persistence of incontinence and difficulties with postoperative catheterization. Persistent incontinence is related to insufficient outlet resistance and/or an abnormal bladder [14–16, 28]. The complications frequently determine the failure of the reconstructive surgery of the bladder neck and compels cutaneous derivation which presently is mainly of continent type [29, 30].

Bladder neck reconstruction in patients who had previous attempts at repair has resulted in less success.

Long-term data according to Kryger et al. favor AMS 800 artificial urinary sphincter (AUS) for surgically managing neurogenic sphincter incontinence in children with no prior surgery of the bladder neck or ure-

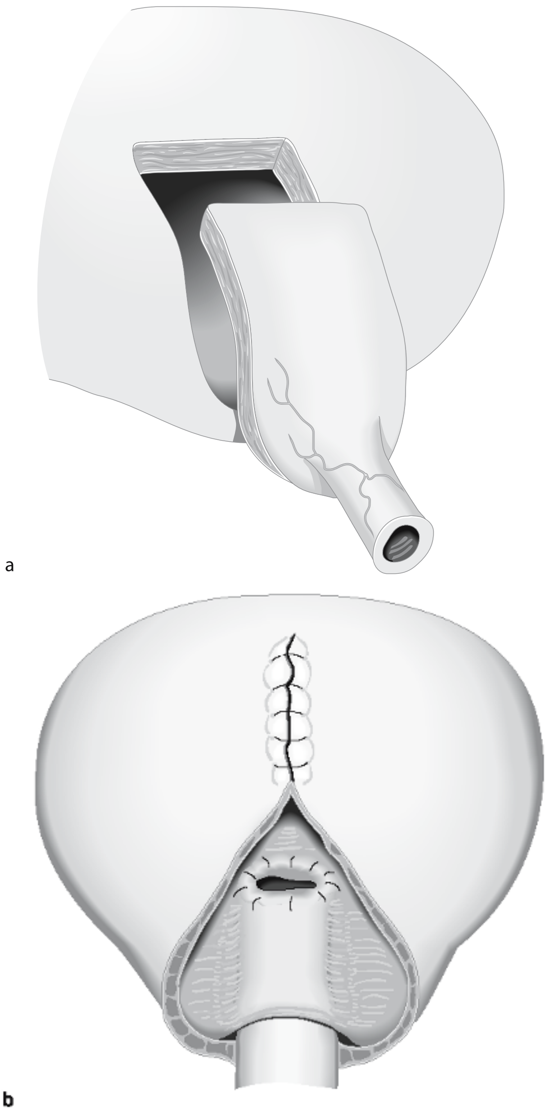


Fig. 3. A Kropp procedure: **a** rectangular bladder pedicle flap is outlined on the anterior bladder wall. **b** The flap is rolled into a tube and then the urethral tube is pulled through a submucosal tunnel.

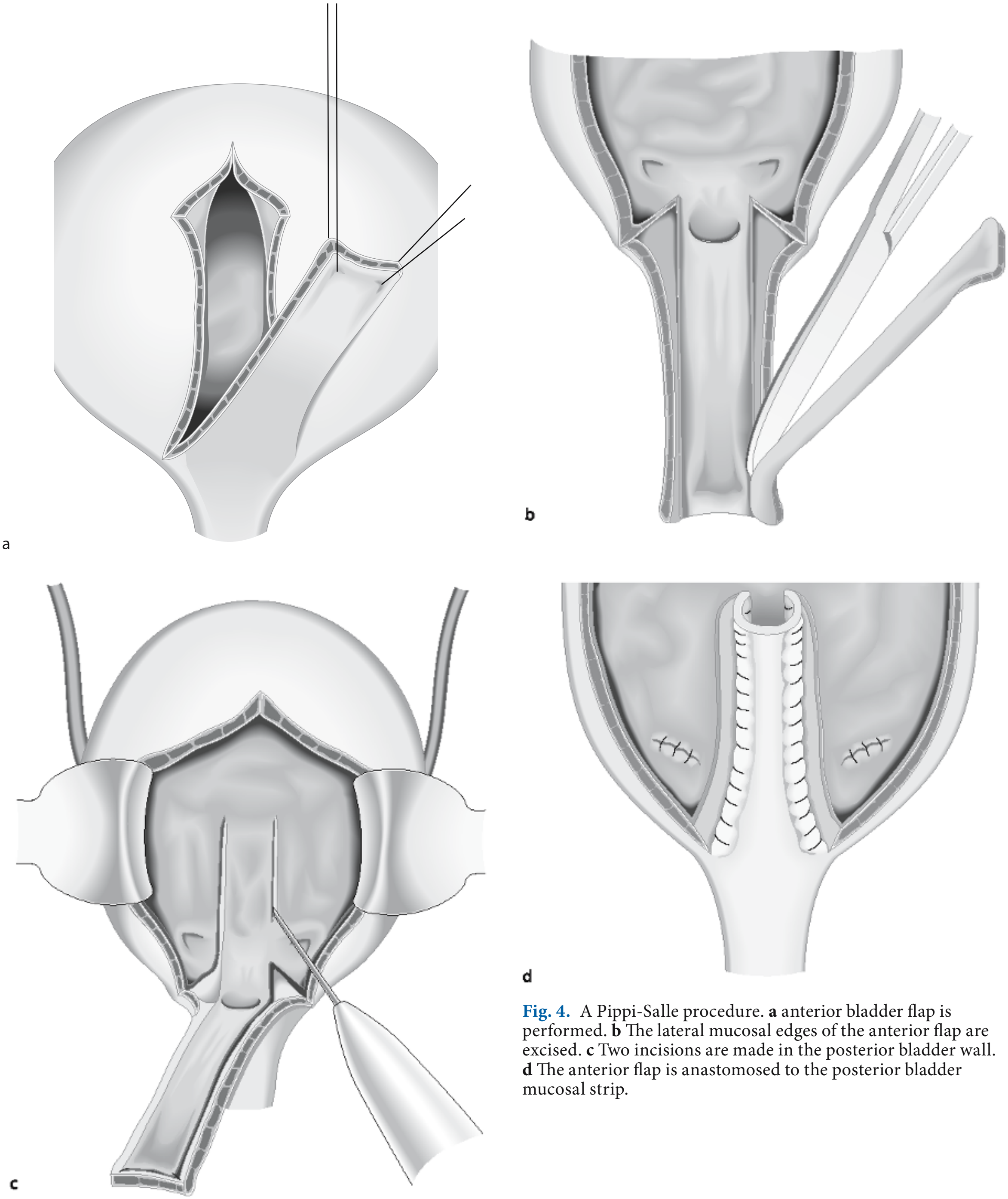


Fig. 4. A Pippi-Salle procedure. **a** anterior bladder flap is performed. **b** The lateral mucosal edges of the anterior flap are excised. **c** Two incisions are made in the posterior bladder wall. **d** The anterior flap is anastomosed to the posterior bladder mucosal strip.

thra. The AUS allows to have a spontaneous voiding, requires augmentation of the bladder in only 40% of cases, and, if necessary, does not interfere with intermittent catheterization [31, 32].

Surprisingly, only 46% of patients could be considered to have a favorable outcome, but with a high reintervention rate for complications such as infection and erosion, or malfunction due to mechanical failure [33].

Other authors also report unfavorable results with the implantation of an artificial urinary sphincter in children with neurogenic bladder. The continence was achieved in 67% of cases, but several surgical revisions (110) were necessary in 63 patients of a multi-institutional study [34]. Furthermore, we have to consider the possibility that the complication rate with artificial sphincters may increase with time. Artificial sphincter is probably again the best solution for selected post-pubertal patients; however, the high cost of the sphincter certainly reduces its use in most countries.

The formal Young-Dees-Leadbetter bladder neck reconstruction has been used for the management of neurogenic incontinence not very frequently; it has normally been applied in the treatment of exstrophy–epispadias complex producing excellent long-term results. Mitchell improved results using modification of the Young-Dees-Leadbetter neck repair. Rink and Mitchell reported a success rate of 57% among 28 patients with meningocele [35]. In the same year Sidi et al. reported a similar rate of continence in 11 patients treated [36]. Donnahoo et al. reported of the 38 patients with neurogenic incontinence 30 (79%) dry and 7 (18%) partially dry. Of the 38 patients, 35 (92%) required bladder augmentation [37].

The Koff procedure provides a good continence but reduces, as all the flap valve procedures, the bladder capacity more than with the YDL repair [11].

The Kropp procedure has provided very good continence rates ranging from 80 to 100% [38, 39], but the procedure has been associated with very frequent catheterization difficulties associated with the risk of spontaneous bladder perforation and the need of bladder augmentation in 100% of cases. Reoperations were required in 19 of the 25 patients primarily because of initial failure to recognize the necessity of providing low-pressure, high-capacity reservoir. The difficulty in passing a catheter was caused by bumps, curves in the bladder tube that deflected the catheter into a blind-ending pocket, or when the bladder became overdistended [40]. The length and angularity of the male urethra increase the potential for complications when boys are catheterized; however, the problems of the catheterization seem to be related to the interruption of mucosal continuity where the tube opens onto the posterior bladder mucosa.

To avoid early problems of catheterization, Kropp proposed to leave the urethral catheter in for 4 weeks [10]. The simplified Kropp bladder neck reconstruction as suggested by Belman and Snodgrass (avoiding the separation of the bladder neck from the remainder of the bladder) also reduces problems with urethral catheterization and general complications [17, 26]. The same Kropp has adopted this modification described by Belman and Kaplan [11].

The modification of the Kropp technique with the use of an onlay of anterior detrusor according to the Pippi Salle's technique preserves mucosal continuity of the urethra with the bladder and allows an easier catheterization [15].

A pop-off mechanism when the bladder is overfilled is observed after Pippi Salle's flap. Patients with a long intravesical tube can have no leakage with an overdistended bladder. The major disadvantage of Pippi Salle and the other flap valve procedures is that the valve will not allow leakage with high intravesical pressures, potentially leading to renal damage [41].

After flap valve procedures, the incontinence can remain on the basis of total or partial loss of the flap, and fistula formation can occur between the proximal intravesical urethra and the bladder. The incontinence related to the formation of urethrovesical fistula and/or partial necrosis of the neourethra in the first case treated led Pippi Salle to develop some modifications of the original procedure, including a widened base to the urethral flap and discontinuation of ureteroneocystostomy as a routine part of the repair [15].

The Salle procedure has reduced the complications, but the continence rates ranged from 67 to 75% [15]. The results have been better in female patients than in male subjects [42].

The fascial sling constructed with the aponeurosis of the anterior rectus muscle is often the best choice in female patients, as it is easy to perform and does not decrease bladder capacity [43, 44]. The sling is used to elevate and compress the bladder neck and proximal urethra. Several technical variations of the sling have been reported, and most authors report a greater success [45–48]. The procedure appears to be less effective in males and is associated with a greater success when used in conjunction with bladder augmentation. Castellan et al. report 88% of good continence in 58 patients treated with a follow-up mean of 4.16 years [49]. Complications include difficulties of catheterization, erosion of urethra. and persistent incontinence [50]. A rectus fascial wrap also in association with YDL cystourethroplasty has been reported [51].

The necessity of the bladder neck surgery to achieve continence in children with a neuropathic bladder has been discussed: In some cases it is possible to achieve continence only by augmentation cystoplasty with no concomitant bladder neck surgery [52].

An ideal technique to increase bladder outlet resistance should be efficient, easy to perform, lead to complete bladder emptying, create an easily catheterizable urethra, use autogenous tissue, not determine loss of bladder capacity, and cause no complications. Surprisingly, no present technique possesses all these criteria.

Personal experience and the possibility of offering different technical solutions according to the case are decisive factors for a successful treatment of urinary incontinence in children with neurogenic bladder.

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Artificial Urinary Sphincter

28

Jean Michel Guys · Geraldine Hery

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28.1
The Artificial Urinary Sphincter: Historical Background

The idea of an artificial urinary sphincter is not a new one. In 1946 Foley made a semi-implantable prosthesis that worked like a pneumatic urethral “clamp”. In 1972 Kauffman proposed a silicone gel prosthesis that would compress the bulbous urethra.

In the attempt to resolve the problem of urinary incontinence, Scott and Bradley again suggested the idea of the artificial urinary sphincter in 1972, almost contemporarily with intermittent catheterization by Lapides. Scott was urged in his research by the serious personal and social difficulties that incontinence implies, the therapeutic failure of urinary diversions, the unsatisfactory results of the bladder neck surgical interventions and the only partial success of intermittent catheterization.

He proposed the use of an implantable sphincter prosthesis, to attain perfect urinary continence and at the same time to improve the patient’s body image and social life. In 1973 Scott published the first three cases that had been treated with this prosthesis. It was still technically rudimentary, consisting of a cuff reservoir and two pumps provided with uni-directional valves, one for the filling of the cuff, the other for its emptying [1].

Simpler models, such as the As 791, indicated for bulbous urethra implants, and the AS 792 for the bladder neck, followed from this first example. The control pump became a single unit; however, the sphincter could be activated only through a second surgical procedure that connected the three constituent elements, and that was generally carried out a few weeks following the implant.

28.2
Present Artificial Urinary Sphincter

The artificial urinary sphincter used presently is the hydraulic model AS 800 by Scott and Bradley [2]. This prosthesis is a system in silicone elastomer, totally implantable, filled with a radiopaque isotonic fluid and made up of three elements: a cuff; a balloon reservoir that generates the pressure; and a pump. These elements are joined by connecting tubes (Fig. 1).

The cuff is a rectangular strip whose internal surface is soft and wide, whereas the external surface is more rigid. One side is joined with one of the connecting tubes, whereas the opposite side is fitted with a buttonhole that permits closing. The cuff may be placed either at the level of the bladder neck or the bulbous urethra, but in children the first solution is usually preferable. The cuff has a standard height of 2 cm, whereas the length varies from 4.5 to 11 cm and is chosen at the moment of implant depending on the anatomic characteristics of the patient.

The control pump is implanted in a position that facilitates manipulation by the patient: in a hemiscrotum in males and in the labium in females. It is 3.3 cm long and 1.2 cm wide. The rigid upper part contains the valves for the bidirectional transfer of fluid and the deactivation button. The lower part, which is soft, is where the patient, using repeated pressure, activates the transfer of fluid.

As mentioned, model AS 800 has a deactivation button either on the upper part of the pump or higher (model

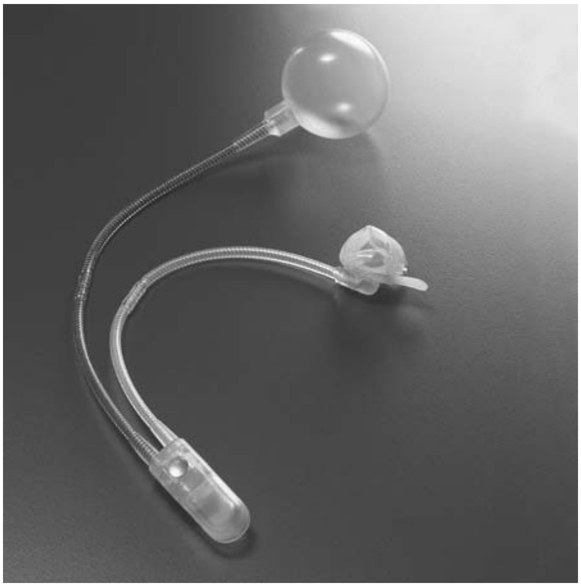

Fig. 1. The prosthesis system is made up of three elements: a cuff; a balloon reservoir that generates the pressure; and a pump

"Securo"), which allows the function and the block of the hydraulic system by means of a simple external manipulation. This feature obviates a further intervention and allows a delayed activation of the sphincter after implantation, allowing full healing to take place. In addition, it makes nightly possible deactivation, which may be very useful in children. This can occur for a longer duration of the sphincter. A temporary deactivation in some cases of bladder problems or infections would also be possible.

The "Securo" model offers the opportunity of implanting a pump made of soft material, thus giving the possibility of using a smaller device in patients who are considered to be too small for the AS 800 model.

Before the implantation, it is important to fully discuss with the patient the side where the pump should be placed in relation to its manual use.

The balloon reservoir is generally implanted behind the rectus muscles of the abdomen in a laterovesical position. This is a clever pressure-regulating mechanism for the fluid inside the system. It is available in four models with a pressure ranging from 41 to 80 cm H_2O. It corresponds to the closing pressure of the cuff, and therefore, it also represents the new cervicourethral degree of resistance. The tubular connections that join the three constituent elements of the artificial sphincter have gradually been made more resistant to possible kinking. They are colour-coded to avoid any error in connections, and the connections themselves are available either straight or right-angled.

The role of the cuff is to compress the urethra or the bladder neck with a pre-established pressure, acting as an extrinsic, occlusive system. When the patient wishes to void, he/she manually compresses the lower, soft part of the pump through either the scrotum or the labium (Fig. 2). This manoeuvre allows the transfer of fluid from the cuff to the balloon reservoir. When the cuff is completely empty, there is no compression and the patient can void. The cuff then refills automatically. As it takes a few minutes for the fluid to return to the cuff, the patient has enough time to empty his/her bladder either spontaneously or by means of a catheter.

28.3 Implantation Technique

The artificial urinary sphincter must be implanted following aseptic technique and with antibiotic therapy pre-, peri- and postoperatively for 48 h. If necessary, urine must be sterilized; therefore, a systematic preoperative urine culture is mandatory in our experience.

Bowel preparation is advisable since most patients suffer from chronic constipation. Moreover, in this way the risk of infection is reduced if a rectal lesion occurs during the intervention. An accurate hair removal should be done just before the operation to avoid bacterial colonisation.

The cuff may be placed around the bladder neck or, in males, around the bulbous urethra. In children, implantation at the bladder neck is always preferred, as, at this level, the risk of erosion is much lower. In addition, in this position, the implant reproduces a physiological mechanism of continence and also diminishes retrograde ejaculation.

28.3.1 Implantation at the Bladder Neck Level

Access is obtained by means of a Pfannenstfiel-type incision with a subperitoneal approach to the bladder. The dissection begun laterally along the bladder neck after tying large lateral veins in the Retzius space. The dissection must be particularly accurate and careful along the posterior plane, where it can be difficult to find the good plane from the rectum or from the vagina [3–6].

In males in particular, a high dissection of the bladder neck just below the ureterovesical junction is advisable. The posterior approach described by Lottman et al. can be useful in some difficult cases [7]. Introducing a rigid, transurethral probe may be helpful, also if used in the rectum or the vagina. Once the circumferential dissection of the bladder neck is complete, it is necessary to extend it in height to about 2.5 cm, corresponding to the size of the cuff. Particular care must be taken regarding haemostasis, to avoid the formation of haematomas which will block the function of the device and favour infection.

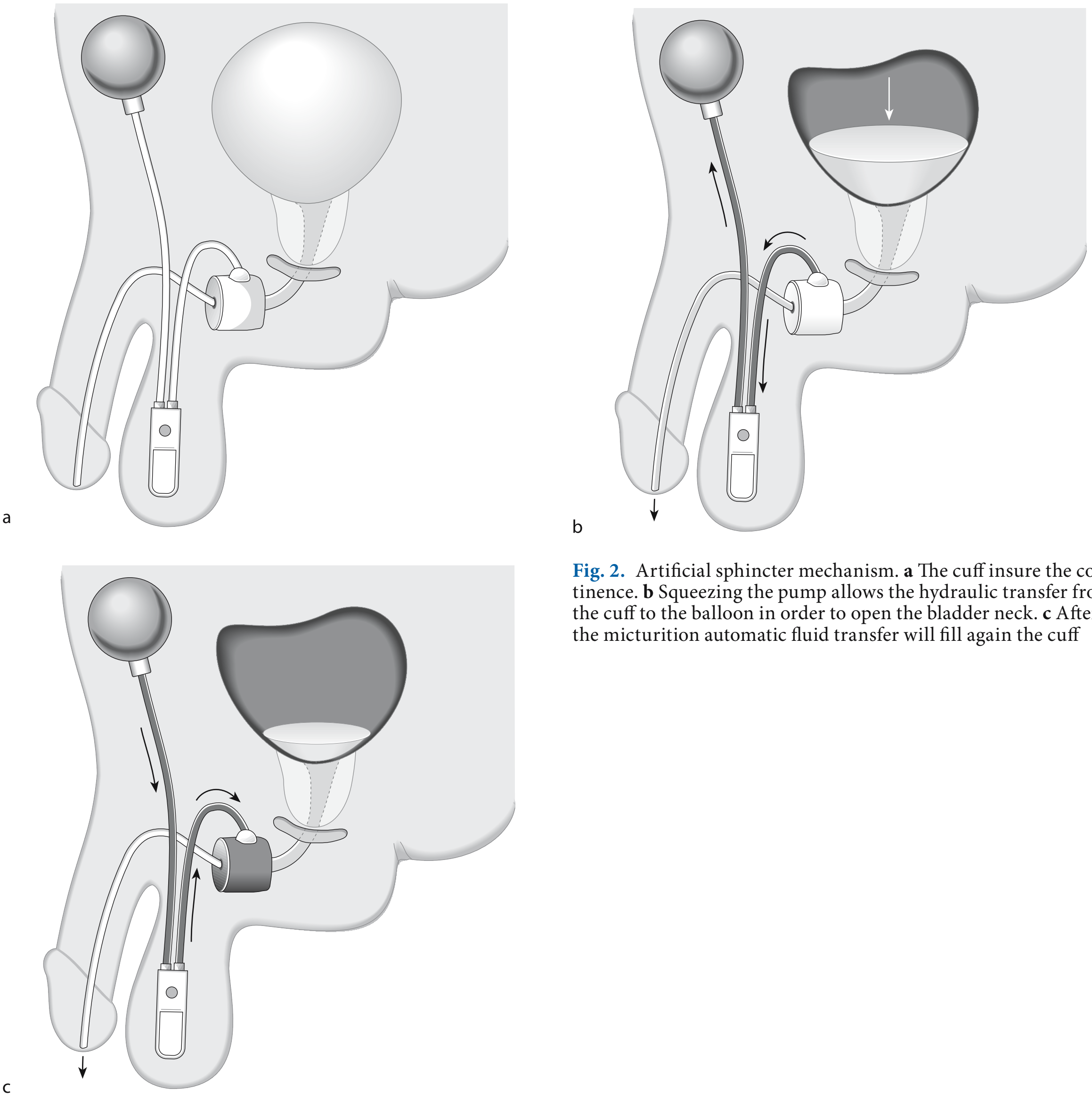

Fig. 2. Artificial sphincter mechanism. **a** The cuff insure the continence. **b** Squeezing the pump allows the hydraulic transfer from the cuff to the balloon in order to open the bladder neck. **c** After the micturition automatic fluid transfer will fill again the cuff

The major risks involved in this intervention is the opening of the vagina, or more seriously, the rectum, which involves the foregoing of the implantation.

The opening of the bladder is not necessary if there is no need for endovesical surgery; however, it is advisable when the dissection is particularly difficult or if there is the slightest doubt of a false passage.

The cuff is chosen after an exact evaluation of the circumference of the bladder neck with the special measuring tape after ablation of a uretral catheter, if placed. The cuff is then placed around the bladder neck and closed anteriorly.

The choice of the balloon reservoir is made on the basis of the preoperative urodynamic data and of the mean arterial pressure of the patient. It is ideal to use the minimum pressure to obtain continence, as this would diminish the risk of necrosis from ischaemia of the bladder neck.

The balloon is placed in the laterovesical space, sufficiently distant from the cuff and the bladder to avoid migration through a pathological or simply fragile bladder wall. This is especially noteworthy if, in conjunction with the implantation, an enterocystoplasty is being performed.

The control pump is placed in the scrotum in males and in the labium in females. This manoeuvre should be as non-traumatic as possible to avoid any haematoma.

The precise location of the pump is important, immediately subcutaneous, to permit easy management by the patient and to easily identify the deactivation button. The connections are made after the system has been filled with isotonic radiopaque fluid. It is essential to

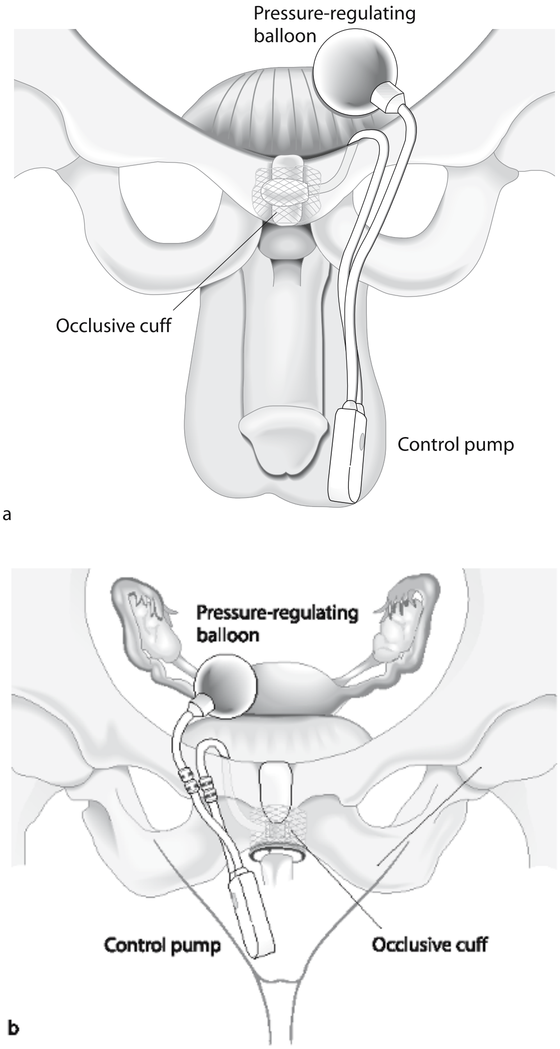

Fig. 3. Implantation of the artificial sphincter at the bladder neck. a In male the cuff is inside the scrotum. b In female the cuff is inside the labia major

eliminate all air bubbles in the preparation of the set for the implantation.

The tubular connections are passed through the belly of one rectus muscle and through the anterior abdominal wall fascia on the side of the patient where the pump will be placed. This facilitates radiological and clinical checks and, above all, a possible further intervention.

Particular attention should be paid to the placement of the tubes so as not to cause any kinking.

A perivesical drain is necessary only if there have been problems with haemostasis during the course of intervention, and then it should be removed as soon as possible.

The bladder is drained with a catheter for 48 h. The usual hospital stay is no longer than 7 days. At the end of the intervention, all the various elements of the implantation are checked radiologically.

The sphincter is deactivated: radiologically, the cuff appears empty while the balloon fills with radiopaque fluid. It is also important to check at this time if there is air in the system, any kinking of the tubes and the correct position of the control pump.

The artificial sphincter is re-activated 15–20 days after the implant, when healing and scarring allow the patient to manage the control pump without any pain.

In younger patients it is advisable to deactivate the sphincter at night: this allows the patient an uninterrupted sleep and most likely contributes to the longevity of the implant materials.

28.3.2
Implantation at the Bulbous Urethral Level

Implantation at the bulbous urethral level is indicated particularly in patients who have suffered destruction to the bladder neck either because of surgical interventions or radiation therapy. Some authors nevertheless report good results with bulbar implantation even in children [8]. But the authors note that, in their experience, it has a long-term survival which rarely exceeds 8 or 9 years.

Implantation at this level is much simpler, but it requires a double surgical access: a small suprapubic incision to position the balloon and the pump and a perineal incision to implant the cuff.

The cleansing and asepsis of the perineum are extremely important. Generally, there is a daily disinfection of the area; urine leakage and cutaneous infections are avoided by using an indwelling catheter for the 7 days that precede the intervention.

The cuff dimension must be chosen very carefully and the advised pressure regime does not go above 61–70 cm H_2O.

28.4
Follow-up

The follow-up of a patient with an artificial urinary sphincter should be both clinical and radiological [4, 6]. It must be a long-term follow-up: in fact, mechanical problems may often occur in the short term, whereas possible deterioration of the urinary tract can be insidious and delayed.

28.4.1
Clinical Follow-up

Clinical follow-up begins with the activation of the sphincter and is repeated 3 months after the intervention. For the subsequent 2 years it is performed every 6 months, then annually.

Continence must be evaluated in many different conditions: at rest; in movement; during sporting activities; and in particular situations (coughing, laughing and defecation). Persistent urinary leakage should be quantified in relation to the methods of protection the patient must adopt.

It is very important to consider the general state of the patient, his reaction to his new “social condition” and possible psychological problems.

During each visit it is necessary to carry out a careful clinical examination which includes the site of the control pump, the connecting tubes and the surgical scar in order to detect possible signs of inflammation or infection.

The manipulation of the pump permits the verification of the proper transfer of the fluid to the balloon. It is also possible to diagnose the presence of air in the system or its transitory block. If the number of compressions needed to obtain pump depression tends to increase, atrophy of the bladder neck may be considered. Contrarily, if there is a diminution, it may signify that the cuff has moved or that there is poor passage of the fluid. If the time taken by the pump to refill becomes excessive, it may be a sign of the presence of organic debris inside the system or a kink in the tubes.

All of these evaluations allow, with just a clinical follow-up, the diagnosis of the majority of early complications.

28.4.2
Radiological Follow-up

The initial evaluation is performed 6 months post-operatively and follows, in the absence of complications, once a year. An abdominal and pelvic echography allow a check-up of renal morphology and the upper urinary tract. This also aids in the research for any possible pelvic abscess, especially those associated with the balloon and the cuff. Ultrasound examination allows the verification of the absence of post-voiding residue and to control the regularity of the balloon and its diameter [9–11].

A plain abdominal X-ray should be executed for each patient, with the artificial sphincter closed and opened in order to see the correct deflation of the cuff.

28.5
Surgical Complications

The principal surgical complications [5, 9, 10, 12–14] are as follows:

1. Infection of the prosthesis that requires its removal (6–9% of cases)
2. Erosion of the bladder neck and/or migration of one of the sphincter components; these also require the removal of the implanted material
3. Atrophy of the bladder neck, often of ischaemic origin, that necessitates a cuff change

The most frequently described (17% of cases) technical errors are:

1. Erroneous choice of cuff size, kinking of the tubes or a wrong connection in the various components
2. The accidental introduction of an organic particle at the initial moment of filling or the persistence of an air bubble inside the system

The prosthesis itself may deteriorate and the following may happen:

1. Breakage at a joint connection
2. A malfunctioning pump
3. A leakage of liquid through the silicone membrane prosthesis due to the fluid not being perfectly isotonic.

After sphincter implantation, it is also possible to experience negative consequences involving the upper urinary tract, usually due to the presence of a serious sphincteric resistance [9, 15–17].

The appearance or aggravation of detrusor hypertonicity or hyperreflexia is often noted (15–45%). In these cases dilatation of the upper urinary tract, with or without reflux, is common.

The appearance of post-voiding residue is frequent enough (18%) to be responsible for infection.

Vesicoureteral reflux may appear over time and is a determining factor in renal deterioration in almost 10% of cases. Deterioration of the bladder capacity leading to a complementary enterocystoplasty is seen in 15–30% of cases; therefore, a long-term follow-up is essential, even in cases that seem clinically excellent [5, 18, 19].

If a further intervention due to mechanical complications is necessary, it should be carried out in a very detailed fashion. Access should be made through the initial surgical site at the level that corresponds to the position of the tubular connections. After clamping the different elements, the quantity of fluid present in the cuff and the balloon is checked. The entire system is accurately checked with the aid of an ohmmeter, which reveals even the slightest leakage.

At this time the defective component should be substituted, with a new verification of the cleanliness of the device, tube connections and control of absence of air inside the system [20]. In our opinion, if the AS has been implanted for more than 5 years, all the components should be changed.

At the end of the surgical revision, an X-ray is carried out in the operating room. In most cases the sphincter is reactivated immediately following the intervention, except in cases where the pump has been changed; then it is advisable to delay the reactivation a few days until all scrotal oedema and pain have disappeared.

28.6
Results

As an example we report herein the results of a homogeneous series of 107 children presenting with neurogenic bladder over a 10-year period: ten French paediatric surgical departments participated in this study [5]. The mean age at the time of artificial sphincter implantation was 13 years, 8 months. Implantation was performed two times more often in boys than in girls. Forty-four percent of patients had undergone previous surgery (28% at the bladder neck) and 27.7% required self-intermittent catheterization. An inflatable cuff was implanted around the bladder neck in 91.6% of the cases. In 24.3% of cases sphincter implantation was associated with other operations. In 58.6% of these cases it was an ureterovesical reimplantation and in 34.5% an enterocystoplasty.

The sphincter was left deactivated for a mean duration of 43 days. Mean postoperative follow-up for the 88 patients with sphincters currently in place was 60.9 months (range 12–118 months). The mean operational life of the sphincter was 56 months (range 3–118 months).

Forty-four patients (40.7%) are totally continent without any revision. Sixty-three patients (59.3%) required a total of 105 revisions due to device-related mechanical problems in 21 cases, surgical complications in 40, and bladder modifications in 40. This relatively high proportion of reoperation must be explained to the patient, and all the series published with a long-term follow-up have pointed out this fact [5, 12, 18, 30].

The most frequent indication for revision was bladder hyperactivity and reduction of bladder compliance (29 cases or 27.1%, vs 20% for non-device-related surgical problems and 18.5 % for device-related mechanical problems) Removal was necessary in 27 cases and was definitive in 20 cases (18.7%). The mean interval of removal was 31.4 months (range 3–104 months). Sixty percent of removals occurred within the first 3 years.

Clinical results were excellent in 72 patients (easy pump operation, complete bladder emptying, total continence with no leakage), good in 10 patients (slight leakage, without pads) and poor in 25. Of the 25 patients with poor results, 20 have required sphincter removal and 5 required more than two pads a day.

The overall success rate was 76.6 %. Eighty-one percent of patients (68 of 84) are continent at 3 years and 86.8% (33 of 38) at 6 years.

No statistical difference in the outcome of implantation was observed between the sexes or according to whether or not the procedure was performed before or after the age of 14 years.

The Indiana experience report on 142 patients with AS shows nearly the same results [18]: success was achieved in 86% of the cases; mechanical complications were noted in 30% of the cases implanted with the model AS 800, revision was mandatory in 16% and bladder augmentation was performed in 22% of the patients after implantation of the artificial sphincter.

The Toronto experience of 79 children concluded with a 90% continence rate for an 80% 10-year survival [21].

28.7
Theoretical Indications for the Implant of an Artificial Urinary Sphincter

The theoretical indications for the implant of an artificial urinary sphincter are as follows:

1. The implantation of an artificial urinary sphincter requires the patient to be autonomous and without significant motor or intellectual handicap. It is essential that the patient be furnished with a detailed explanation of the mechanism and of the possible complications of the sphincter in such a way to obtain the best possible comprehension of its function and way of use; therefore, in our opinion, it should not be implanted before 10 years of age, although some American surgeons have begun implantations in children as young as 5 years. Kryger et al. specify that the long-term results appear independent of patient age at the time of placement (before or after 11 years) [22]. Puberty is probably the best period for the implant, as physical development is almost complete and the natural evolution of the neurological bladder can be considered near its conclusion.
2. The family environment is an important factor. There is certainly an adjustment period learning how to use the prosthesis, the obligations that are associated with it (regular bladder emptying) and the new habits that continence may imply. During this phase, good family knowledge and support are considered secondary factors for the success of the implant. Be that as it may, deep motivation on the part of the patient is an essential element in obtaining therapeutic independence as soon as possible [4, 6].

3. The patient must not have evolutive renal lesions. Any type of change in the upper urinary tract must be considered stable. It is particularly important that there be no evidence of vesicoureteral reflux or any type of pyelic or ureteral obstruction. From this viewpoint, the concept of normality of the upper urinary tract, expressed by the majority of articles that focus on this subject, must therefore be understood as preserved renal function. Many patients with neurological bladder, in fact, show an alteration of the upper urinary tract. Again, it is essential that the reflux or the obstruction be corrected.
4. The bladder must have good capacity and compliance, low pressure and have no signs of hyperreflexia. These conditions must be completely satisfied before implanting an artificial sphincter. It is noteworthy that many late failures reported in the literature are attributed to the decrease of functional bladder capacity, the appearance of uncontrollable hyperreflexia or the progression of evolutive detrusor lesions [5, 9, 18, 21]. Good tolerance to intermittent catheterization for the neurological bladder has allowed the role of an augmentation enterocystoplasty to be brought into the forefront. The enterocystoplasty, using any part of the digestive tract (sigmoid, ileum, stomach), permits the bladder capacity to reach a more than satisfactory level, and in some cases to interrupt the vicious circle of refractory hypertonicity and hyperreflexia to anticholinergic therapy [18, 23, 24]. The presence of an enterocystoplasty is not a contraindication for an artificial sphincter implant; on the contrary, it may provide the determining factor for a positive result [13]. In these cases it is necessary to rely on intermittent catheterization to empty the reservoir, but this does not represent an additional risk factor. The simultaneous execution of an enterocystoplasty and a sphincter implant is not advisable for long periods because of the possibility of additional risks of infections [25]. On the other hand, recent experience tends to contradict this conviction [23].
5. The patient who is a candidate for an artificial sphincter must have a urethra that can be easily catheterized. It is, in fact, essential to obtain regular evacuation for whatever type of bladder, and to be able to rapidly treat acute urinary retention or post-voiding residue that may appear after the implantation of the artificial sphincter. Sometimes, it is necessary to perform an augmentation enterocystoplasty in a second stage which obviously requires intermittent catheterization to avoid post-voiding residue. On the other hand, a sphincterotomy, which has been widely advised, does not seem essential to the present authors. Even though urethral resistance is lowered further and post-voiding residue diminishes, as does endovesical pressure during micturition, our concern is that it is too definitive a procedure and therefore we do not recommend it in the paediatric age.
6. A previous surgical intervention on the bladder neck does not represent an absolute contraindication to an artificial urinary sphincter implant. In fact, in some articles, it does not seem to be the cause of many additional complications [26]. This, however, should be carefully evaluated, as it may be a determining factor for difficulties and risks during the dissection of the bladder neck. This concern does not include the Young Dees technique, which actually reinforces the quality of the bladder neck especially along the anterior side. Instead, it certainly concerns the suspension-type interventions that require a posterior dissection of the bladder neck, which makes in thinner and may lead to erosion. Moreover, a previously surgically treated bladder neck may become fibrous and therefore less sensitive to the compressive action of the artificial sphincter, which is, undoubtedly, a negative factor for continence.
7. The gender of the patient may also be an important factor in the choice of technique to increase sphincter resistance. In fact, in our opinion, the artificial urinary sphincter should be proposed as a first operation more often in males than in females. For the female group, it seems that operations, such as a bladder neck reconstruction or suspensions, are more easily carried out and are effective [27] – even if, in female patients, AS 800 is considered by some authors to be a first-line treatment [28, 29].

Immediate good results must not obscure the fact that specific complications of the artificial sphincter often show up after years of perfect function of the prosthesis [8].

28.8
Conclusion

The artificial urinary sphincter may be considered one of the methods of choice for the treatment of neurogenic urinary incontinence. In paediatric practice, however, it should not be proposed gratuitously for patients with sphincteric deficits. Obtaining continence is simple if the indications and the technique of implantation are given their due consideration.

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Enterocystoplasty

29

David C.S. Gough · Jean Michel Guys

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29.1
Introduction

Small or large intestine has been used for more than a century either to enlarge the bladder in rare conditions such as bladder exstrophy, or as a bladder replacement or substitution in patients with tuberculosis. Therefore, it had relatively limited application and gave extremely disappointing results because of poor bladder emptying. Complications, such as infection and upper tract damage, were common; long after the antibiotic era commenced, urinary incontinence both by day and night limited the appeal of substitution or enlargement cystoplasty [1]. Several factors then coincided, which led to the sudden and widespread use of bladder augmentation in treatment: the introduction of clean intermittent catheterization which had been established as a safe efficient method of emptying the bladder [2]. The appreciation that the lower urinary tract had the potential for causing upper tract deterioration in the neuropathic bladder, and in the state of chronic retention. The widespread introduction of urodynamics as an investigative tool led to the appreciation that pressure was the problem [3, 4]. In addition, urinary diversion with a conduit had been the mainstay of management for patients with a neuropathic bladder, but it became apparent that the long-term results were far from satisfactory [5]. Perhaps it was the survival of a large cohort of patients who had been treated for spina bifida and who were under urological observation that led to an appreciation that these patients had progressive upper tract change either from their underlying pathology or their treatment. At this point a simple form of cystoplasty was introduced by Bramble which was subsequently shown to be an effective augmentation technique [6]. As with most new surgical procedures there was a period of initial enthusiasm, in which the procedure was reported from around the world, followed by many modifications of the technique [7, 8]. This phase was followed by a lengthier appraisal of the complications and problems as they began to manifest, after which there was a period of reappraisal [9–11]; however, when cataloguing the problems after enterocystoplasty the procedure must be put into context and compared with the alternative forms of treatment. Without some form of treatment these patients, who have high pressure urine storage, will have urinary incontinence and severe UTI. With no treatment they will have progressive upper urinary tract deterioration and, not infrequently, will die from renal failure [12]; therefore, at each stage where the outcome and the value of enterocystoplasty is discussed, there is a need to be cognisant of the complications of the alternative techniques, e.g. urinary diversion, use of indwelling catheters or diversion via ureterosigmoidostomy.

29.2
Technique

Intestinal segments from the jejunum through to the sigmoid have been used for enterocystoplasty; however, jejunum quickly fell into disrepute because of particular problems with water re-absorption. Ileum can be used in the form of a cup or simply as a detubularized segment. The ileocaecum [6, 13–15], the caecum and the sigmoid colon are all alternatives[16, 17].

29.2.1
Surgical Technique

This section describes enterocystoplasty using the sigmoid colon, which is the most frequently used technique in our department. Preoperative bowel preparation consists mainly of a low-residue diet for 5 days prior to the procedure in association with enemas in the morning and evening of the final 2 days and administration of an oral washout solution such as Golitely on the final night. In most cases an oral antibacterial agent for digestive tract infection, such as Flagyl, is administered 48 h (2×30 mg/kg) before the procedure.

The procedure is carried out through a median laparotomy made from the umbilicus to the pubis usually using the Pfannestiel-type incision. Initial exposure of the bladder is achieved through the subperitoneal space followed by complete extra-peritonization of the bladder dome and its posterior part to the trigona. Longitudinal cystostomy through the midline of the anterior part of the bladder is performed to allow assessment of the position of the ureteral meatuses and the quality of the submucosal channel of the ureters. If preoperative cystography has demonstrated evidence of reflux, we prefer to perform ureteral reimplantation usually using the technique described by Cohen; however, many authors consider that reflux will resolve if enterocystoplasty is successful in reestablishing low intravesicular pressure. If required, repair the bladder neck can also be performed.

The bladder should be completely divided into two parts using the clam-shell technique (Fig. 1a). Division of the bladder is important for three reasons. The first reason is that it facilitates augmentation by providing a large area for anastomosis between the bladder and the sigmoid colon; the second is that it allows attachment of the bladder to the psoas muscle, thus facilitating reimplantation of the ureters. The last reason is to avoid the need to reshape the sigmoid colon because of the large surface of the split bladder.

After approximate measurement of the circumference of the bladder, the peritoneum is opened and a segment of the sigmoid colon of a similar length (usually 20–25 cm) is isolated along with its vascular pedicle (Fig. 1b). The segment is opened along its anti-mesenteric margin so as to obtain a rectangular-shaped patch. If a Mitrofanoff stoma is required and the appendix is unuseable, isolation of the sigmoid colon can be associated with a Monti-type procedure to create an additional tube with its own vascular pedicle. Intestinal continuity is re-established by end-to-end anastomosis. Extraperitonization of the sigmoid colon patch is performed through a small breach in the pelvic peritoneum and the augmenting segment is anastomosed to the bladder with absorbable sutures.

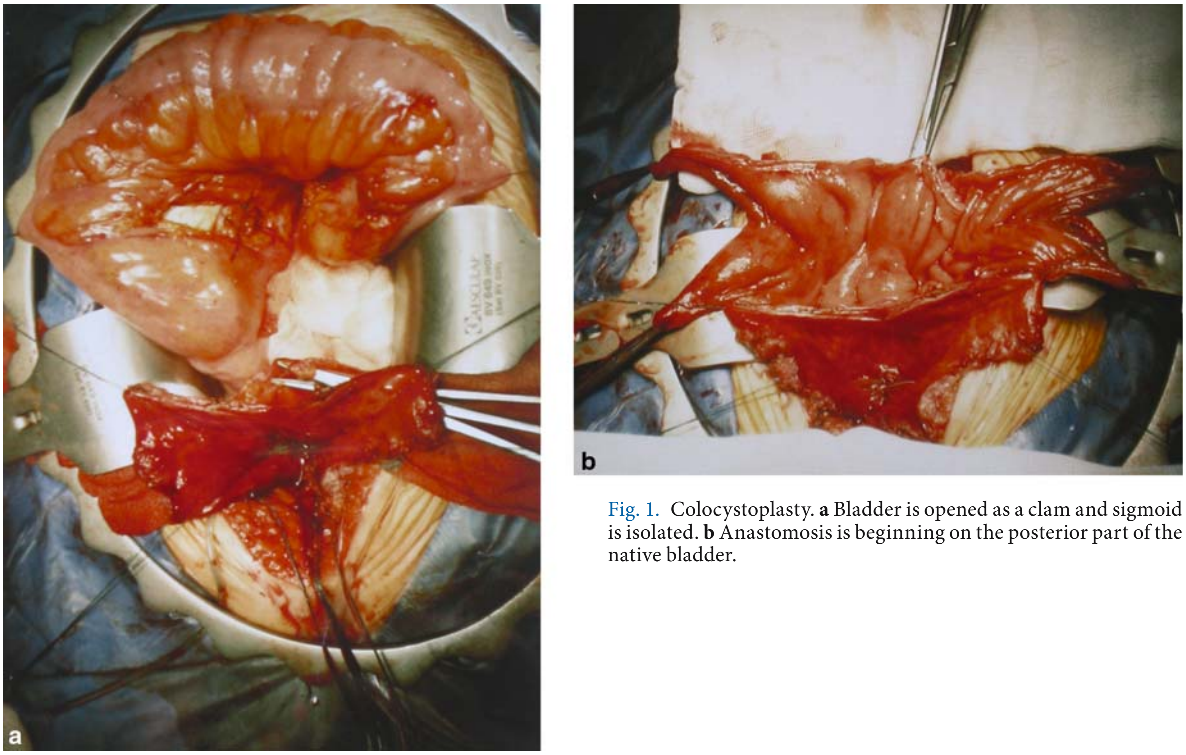

Fig. 1. Colocystoplasty. **a** Bladder is opened as a clam and sigmoid is isolated. **b** Anastomosis is beginning on the posterior part of the native bladder.

Postoperative care following enterocytoplasty care includes drainage for 10 days and bladder irrigation in the early postoperative period. Drainage should be performed not only through the uretra but also through the wall of the bladder in order to have two ways of drainage. Transparietal drainage can be performed using a Mitrofanoff-type conduit if it exists or has been created during the operative procedure. Drainage must be performed using at least 14-cm-diameter silicone catheters in order to prevent retention of mucus that may lead to obstruction of the drainage catheters, if too small.

It is traditional practice in the early phases after cystoplasty to prescribe antibacterial prophylaxis in the form of Trimethoprim 2 mg/kg per day or Naladixic acid 25 mg/kg per day or Nitrofurantoin 1 mg/kg per day, but whether this needs to be continued long term has not been established, and most authors would consider it safe to cease such treatment once a successful cystoplasty has been established. It is our experience that progressive enlargement of the cystoplasty occurs over the first 6 months following surgery, and we suggest that it is reasonable to stop antibiotic therapy at this point.

29.3
Post-Operative Follow-up

Renal ultrasonography is carried out 1 month after the procedure to rule out pyelic or ureteral dilatation. This follow-up examination is especially important in patients who undergo associated reflux treatment. Cystography, thorough urodynamic study, and repeat renal ultrasonography are performed 6 months after the procedure (Fig. 2). Long-term follow up including the same examinations as at 6 months should be done on a yearly basis. Bladder lavage is necessary two to four times per week during the first month and then as required depending on the condition of the urine.

The place of prophylactic antibiotics in patients who have had cystoplasty and who are emptying the bladder by catheterisation has not truly been established. Many patients cease takin prophylactic antibiotics in the long term and the incidence of infective complications does not seem to change significantly.

29.4
Surgical Complications and Side Effects

29.4.1
Post-Operative Surgical Complications

Cystoplasty procedures require access to the peritoneal cavity to obtain material for the augmentation, and this carries with it a risk of postoperative complications, the most notable of which is intestinal obstruction from adhesions. Where long-term follow-up has been established this can be present in approximately 10% of patients undergoing ileocystoplasty [9]; however, when compared with a series of children who had had ileal conduits, this long-term surgical complication becomes insignificant, as 10–16 years after urinary diversion only 12 of 75 children who had had a conduit constructed had not had at least one surgical complication [19]. Adhesion obstruction can occur in the early or late phase after cystoplasty and there are dangers in re-operation, as the

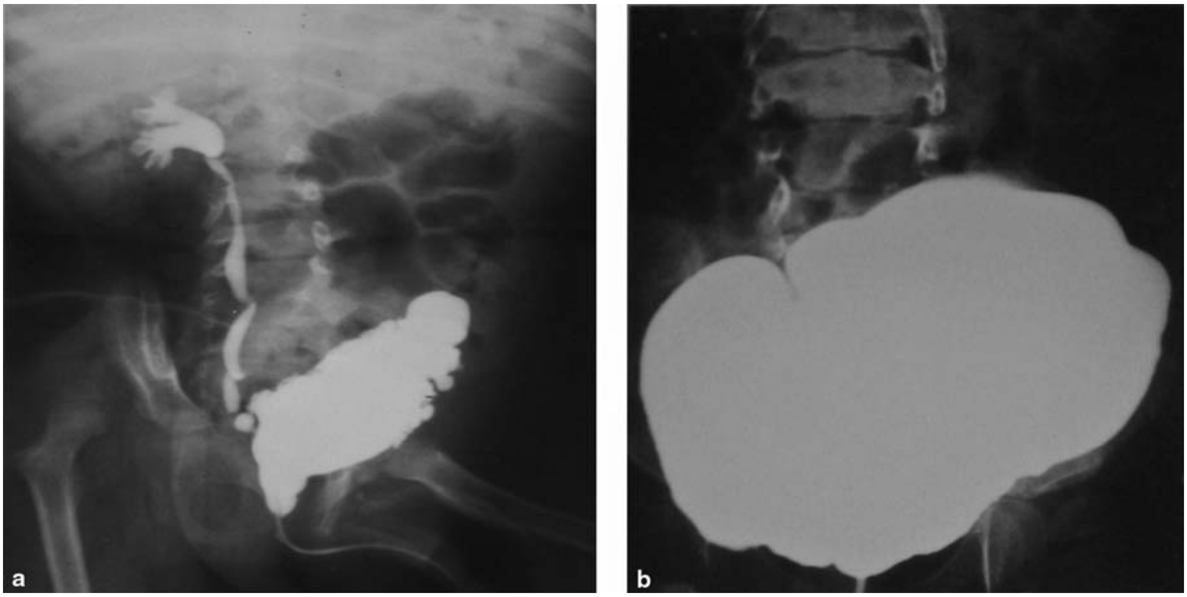

Fig. 2. Cystography **a** pre- and **b** post-enterocystoplasty

vascular pedicle of the cystoplasty is vulnerable during a laparotomy. Clot or mucous obstruction of the catheters can lead to urinary extravasation in the early postoperative period, and this is normally controlled by external drainage established at the initial procedure, anticipating such a problem.

29.4.2
Perforation

Perforation is one of the most serious and life-threatening complications of enterocystoplasty, and seems to occur with equal frequency whatever piece of intestine has been used. The perforation is usually in the bowel segment or through the anastomosis to the native bladder; it occurs in 5–10% of patients [9, 20]. The cause of the supposed increase in pressure which is thought to underlie the perforation can most often be related to a failure to catheterise; however, high-pressure detrusor contractions have been cited as a potential cause [21]. Other factors which may be involved are related to the absence of sensation and the possible direct perforation from a bladder catheter.The diagnosis is usually made from a combination of sudden peritonitis or lower abdominal pain associated with low-grade fever and evidence of urinary extravasation on ultrasonography, either into the local pelvic tissues or the peritoneal cavity. A formal diagnosis by cystography is usually undertaken but perhaps leads to an under-diagnosis in approximately 20% of patients [22]. Where major extravasation has not been detected on cystography, then catheter drainage can lead to successful resolution, and in the authors' experience does so in more than half the patients; however, patients with severe shock who fail to respond to resuscitation, and in whom there is a significant delay in diagnosis, can deteriorate rapidly and die [20].

29.4.3
Urinary Tract Infection

Patients with high-pressure urine storage or with significant residual urine volumes have a high incidence of severe symptomatic UTI before surgical treatment with enterocystoplasty [12]. When CISC is used to empty a neuropathic bladder which does not require augmentation nearly half the patients have chronic or recurrent UTIs [23]. This problem does not seem to respond to prophylactic antibiotic treatment [24]; however, after enterocystoplasty, despite the continued need for CISC, there are dramatically fewer episodes of symptomatic UTI. Furthermore, febrile episodes requiring hospitalization are most infrequent [12, 25]. There may indeed be beneficial effects of an ileocystoplasty in this situation, in addition to lowering the intravesical pressure, in that secretory IgA levels have been found in high concentrations in the urine of patients after a cystoplasty. This may improve the patients defences in preventing adherence of bacteria to epithelial cells and thence systemic involvement [26]. In this regard the incidence of significant infective complications after cystoplasty seems to mirror that seen in patients with an ileal conduit or indwelling urinary catheters, but is far less than that seen after ureterosigmoidostomy [27].

29.4.4
Stone Disease

Lower urinary tract stones are common after augmentation cystoplasty and seem to occur with increasing frequency as the follow-up lengthens. Stones can cause bladder irritation and present with incontinence, haematuria or urinary infection, but are often found on routine annual ultrasonography of patients who have had an augmentation cystoplasty. They are difficult to remove in toto when the patient has a continent diversion with an abdominal stoma; open removal is most likely to free the patient of their stone burden. To date, in the author's experience, of the patients who developed stones there is a 30% risk of further stone formation within a 2-year period. The incidence of stone disease is much higher in patients who have had a continent diversion and stones seem to appear early after surgery in most; however, this may simply reflect the short-term follow-up. The presence of mucus after the cystoplasty has been implicated in stone formation, as this binds calcium from the urine and can form the nidus of stones. The retention of mucus within the bladder, particularly after continent diversion and the use of a Mitrofanoff stoma, probably leads to the higher formation of stones in these patients; thus, some surgeons choose to site the Mitrofanoff stoma as low as possible on the abdominal wall, to aid the siphon effect during bladder catheterization. Washing out the mucus regularly, e.g. weekly, does not seem to prevent stone formation and it may be necessary to wash the bladder daily if the incidence in some patients is to be decreased [28]; however, upper urinary tract stones are common in patients who have undergone urinary diversion and can occur in up to 30% of patients after colonic conduit diversion [29].

29.4.5
Mucus Production

Mucous problems are fewer with ileocystoplasty and the mucus production improves with time. This is less likely to occur after sigmoid cystoplasty. The amount of mucus produced can also respond to dietary manipulation. Reducing the intake of dairy products and onions, or adding cranberry juice or cranberry capsules to the diet, is said to reduce the amount of mucus produced [30].

29.4.6
Effects from Shortening of the Gut

Removing such relatively modest parts of the intestine might be considered to have no effect on overall gastrointestinal function; however, effects on bowel function can be profound, with 30% of the patients having long-term problems of increased frequency, with a quarter of neuropathic patients having increased fecal incontinence after enterocystoplasty [31]. If large segments of the terminal ileum are used it can lead to vitamin-B12 deficiency, and long-term follow-up for the haematological complications of this disorder will be necessary [32].

29.4.7
Metabolic Complications

When bowel mucosa comes in contact with urine there is specific reabsorption of water, sodium, hydrogen ion, ammonium and chloride, and increased loss of potassium and bicarbonate into the urine. This leads to hyperchloraemic metabolic acidosis [33, 34]. Water balance is most significantly affected when the jejunum is used and hyperchloraemic alkalosis worsens when the urine comes in contact with large bowel mucosa. This imbalance is seen most frequently in patients who have undergone uretero-sigmoidostomy [35]. Despite this, most patients after enterocystoplasty are asymptomatic and the complication rate of metabolic acidosis seems to be equivalent to that seen after ileal diversion. Where symptoms occur, oral bicarbonate therapy is given. The chronic acidosis can cause bone disease [36]. In the neuropathic population, most of whom have spina bifida, it may be difficult to determine the contribution made by the cystoplasty to the overall orthopaedic burden of complications that these children have. Similar biochemical complications are seen in patients who have a Kock pouch or a long ileal conduit. Once the patient has reached adult life, then the bony complications seem to be less of a problem [37].

29.4.8
Neoplasia

Carcinoma occurring as a late complication of ileocystoplasty has been known for some time [38], but it has been difficult to determine whether this is caused partly by the underlying disease. The bowel segment used for the cystoplasty does not seem to be relevant and when neoplasia occurs there is significant mortality, which can be approximately 30%. Of 16 patients reported, 13 had tuberculosis or chronic cystitis as the underlying condition, which led to an ileocystoplasty [39]. Another factor that may be involved in the development of malignancy is the production of urinary nitrites by bacterial infection. The carcinogenic effects of this and nitrosamines have been implicated in tumours seen in urinary conduits and for those occurring after ureterosigmoidostomy [40]. Malignancy in patients with neuropathy and structural malformation such as bladder exstrophy seems relatively rare and compares favourably therefore with the incidence of malignancy in ileal conduits assessed in the long term. Where an alternative form of treatment such as ureterosigmoidostomy has been available the results suggest a much higher risk of developing adenocarcinoma at the uretero-sigmoid junction. There seems little prospect of easily detecting the early development of malignancy, which has been known to occur within the first 5 years after an ileocystoplasty (I. McIntyre and D. Brooman, pers. commun.). There is a suggestion that urinary cytology should be assessed every fifth or tenth year, but chronic bacterial infection induces infective change in the mucosa, which makes the diagnosis of centrifuged sediment very difficult [41].

29.4.9
Incontinence

Incontinence is not necessarily a feature of the cystoplasty but reflects an inadequate continence mechanism. Despite careful assessment most surgical units find that continence is less than perfect in ≥15% of their patients [42]. These results are inferior to those from an ileal conduit, despite that in some patients the bag will become displaced or provide an imperfect seal, or the stoma will need to be revised as it flattens or retracts, or even prolapses over time.

29.4.10
Conclusion

Despite the problems of augmentation cystoplasty, on balance it has been a much better form of management of the lower urinary tract in patients with bladder neuropathy or high-pressure detrusor contractions than the alternatives of rectal diversion, indwelling catheter or external urinary diversion. The metabolic consequences do not seem to interfere with general health in the medium term. The risk of perforation appears to be present with other forms of augmentation cystoplasty or bladder replacement; however, the results are far from perfect and the ideal technique will be one that:

1. Removes the need for intraperitoneal surgery and prevents the risk of intestinal adhesions
2. Stops the development of intestinal mucus and stone formation
3. Prevents the metabolic complications and potential bony complications during adolescence
4. At the same time improves the patient's resistance to UTI
5. Maintains the same degree of long-term, good, low-pressure urine storage and the consequent improvement and stability of the upper urinary tract.

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Gastrocystoplasty

30

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30.1
Introduction

Bladder augmentation means the creation of a urinary reservoir made up of the original bladder, or part of it, and a part of the gastrointestinal tract (stomach, ileum, caecum, sigmoid colon) "isolated" and anastomized to the bladder [1–4]. The urethra is conserved and the ureters are usually re-implanted into the bladder.

At first this type of surgery was used exclusively for adult patients affected by vesical tuberculosis, vesical carcinoma, interstitial cystitis or in patients with neurogenic bladder; however, this technique has recently been used for the reconstruction of the urinary tract in younger patients affected by complex urogenital malformations or by neurogenical bladder [5, 6].

Until about 20–25 years ago many of these conditions were treated with an "external" urinary derivation or, in some selected cases, an "internal" one. The past few years have, however, seen the preference of reconstructive surgery of the inferior urinary tract by means of vesical augmentation or substitution (rare in paediatric age), containing urinary derivations, reconstructions of the vesical neck and proximal ureter.

It is important to emphasise that these methods are possible thanks to the proved efficacy of clean intermittent catheterization (CIC) introduced by Lapides in the 1970s [7]. This procedure allows the passive drainage of a constructed reservoir and, in the cases in which spontaneous urination is foreseen, has an important re-educative role.

It is also important to stress the selection of the patients in as much as this type of surgery is an alternative to external derivation, and avoids the use of external urine collection sacs but forces a passive drainage of the new reservoir (CIC); therefore, it is necessary to evaluate the physical limitations as well as the family and social/psychological limitations of the patients who are candidates for this type of surgery, and to indicate, other than the advantages, the risks linked to a containing urinary reservoir that is not correctly managed.

In paediatric age and adolescence the indication for vesical augmentation is proposed when there is a small, inelastic, incontinent bladder with high internal pressure, conditions that can cause a worsening of the upper urinary tract due to stasis or secondary reflux [8]. The conditions of this type are:

1. Neurogenic bladder (spina bifida)
2. Major malformations: estrophy–epispadia complex, posterior urethra valve, estrophy of the cloaca
3. Vesical fibrosis secondary to radiotherapy
4. Single bilateral urethral ectopia
5. High degree vesico-ureteral reflux with small inelastic bladder secondary to chronic phlogosis (rare)

30.2
Historical Notes

Different intestinal segments (ileum, caecum and sigmoid) are involved in vesical augmentation, but each has its own problems: excessive mucus production; hypercloremic acidosis due to absorption of ammonium chloride; urinary tract infections (UTI); vesical stones; nutritional deficit; spontaneous perforation of the patch; and risk of malignant degradation [6, 8, 9].

In 1956 Sinaiko [10], for the first time, proposed the use of the stomach. This technique was then re-proposed by Leong and Ong [11, 12], and by Rudick et al. in the 1970s [13], without being unanimously accepted.

In an experimental model, Piser et al. demonstrated the barrier function of the gastric mucosa: it does not reabsorb chloride and ammonia ions, but can release chloride ions [14].

Lastly, Kennedy [15] and Sanni-Bankole et al. [16] showed the metabolic advantages of the gastric patch, with respect to the intestinal patch, in dogs that had undergone a vesical augmentation and who had metabolic acidosis.

In the 1980s Mitchell re-launched the use of gastrocystoplasty (GCP) on a large number of paediatric patients and established the technique reporting excellent results [14, 17–19].

30.3
Advantages of Gastrocystoplasty

In theory, the advantages are numerous for the choice of the gastric patch with respect to other intestinal segments:

1. Absence of macroscopic mucous deposits
2. Fewer infections of the urinary tract due to the tendentiously acidic pH from the production of chloride ions
3. No stone formation and less metabolic disorders as the gastric physiopathology helps prevent hypercloremic metabolic acidosis.

The mechanism responsible for the metabolic advantages, in fact, is linked to the barrier action of the gastric patch, which not only impedes re-absorption of ammonia and chloride but also releases these ions that play an important role especially in cases of chronic metabolic acidosis [14].

Another element in favor of the gastric patch is the notable reduction of UTI, unlike what is generally found in enterocystoplastic [20, 21].

In GCP urine is generally sterile, which could be due to the acidity from gastric secretions and the elimination of substances with antimicrobial effects from the gastric patch [9]. On the other hand, the absence of mucous and infections in the urinary tract could underlie the lower number of stones formed in patients treated with GCP [22].

Finally, the gastric wall is robust and resistant enough to allow a ureter reimplantation that is technically more simple, other than reducing drastically the risk of spontaneous perforation or secondary to intermittent catheterisation.

All these advantages make the gastric segment a privileged choice in vesical augmentation, even if in some patients the choice of this gastric segment is obligatory as it is linked to the type of pathology:

1. Patients in whom another intestinal segment is not useable as they are already undergoing radiation therapy or with a short intestine (estrophy of the cloaca, etc.).
2. Patients with metabolic acidosis. This condition could be aggravated by the use of an intestinal segment that absorbs chloride and ammonium ions.

30.4
Surgical Technique

The surgical technique used is that described by Adams et al. in 1988 [17]. Pre-operatory examinations include the following:

1. Serum electrolytes, urea and creatinine level
2. Ultrasound scan, renal scintigraphy (technetium-99 MAG3 or DMSA)
3. Cystourethrogram with measurement of the vesical capacity, and, if possible, a urodynamic study
4. Radiological study of the stomach

There is no need to have a specific intestinal preparation, while intestinal antibiotic prophylaxis is advised, as in all cases of major surgery in paediatric age. Treatment with anti-H2 begins 2 weeks before surgery.

After the xipho-pubic incision, the bladder is explored through a large incision on the median line that goes from the anterior vesical neck to the posterior of the trigone. The ureteral reimplantation, when necessary, is carried out at this point according to Cohen's or Politano-Leadbetter's technique.

The exploration of the stomach follows. The gastroepiploic arteries are evaluated to exclude eventual

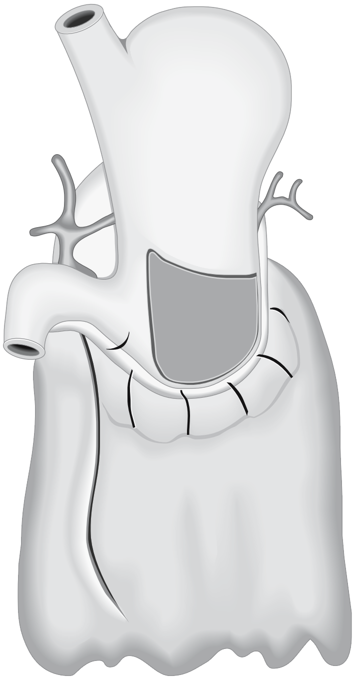

Fig. 1. Preparation of the gastric patch

anomalies. The limits of the triangle that will be the gastric patch are made: the apex is towards the small curvature and the base corresponds to the large gastric curve (Fig. 1).

The triangle is drawn making reference to the point where the left and right gastroepiploic arteries pass, defined on the large curvature by a different orientation from the gastric vessels, and chosen so as to reduce the gastric body, saving the antral part, and avoiding damage to the gastric trunks of the vagus nerve, which run parallel to the small curvature at about 1–1.5 cm from it. The patch measures from a minimum of 8 to a maximum of 12 cm, in correspondence to the base of the triangle on the large curvature, whereas the isosceli sides measure from 7 to 9 cm.

Generally, the vascular peduncle used is given by the right gastroepiploic artery. It is necessary to close all the vessels of the large omentum and its successive opening at about 2 cm from the large curvature protecting the gastroepiploic vessels. The stomach is then sectioned for all its thickness, with straight autosuture staplers with the double aim of avoiding the dispersion of gastric juice into the peritoneum and to obtain a more rapid haemostasis. The irrigation of the gastroepiploic artery with papaverina obviates spasm.

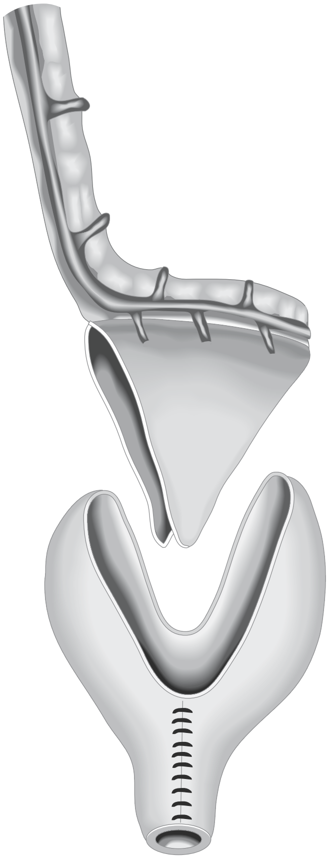

Fig. 2. Triangular segment of the stomach pedunculated and positioned on the bladder

The triangular segment of the stomach is pedunculated on the right gastroepiploic vessels (artery and vein; Fig. 2) and must be protected from mechanical and thermal stress while the gastric wall is reconstructed, after the removal of any metallic staples, with a continuous suture of the mucosa and submucosa, reinforced by interrupted seromuscolar suture. A nasal–gastric tube is positioned in the stomach before the definitive closure of the anterior wall.

A transmesocolic and retroperitoneal tunnel is created in which the vascular peduncle of the gastric patch will run, which, from the sovramesocolic space, will pass into the pelvic pouch, exiting near the bladder above the right ureter.

At this point, a cystogastric anastomosis can be made by means of short continuous blocked sutures with reabsorbable 3/0 thread in a single mucous, muscular and serous layer.

Before the definitive closure of the bladder, the following are positioned: the ureteral stents; a vesical Foley-type catheter; and a sovrapubic catheter (Cistofix or Pezzer). The retroperitoneum is closed and the intestinal loops are re-positioned in the abdominal cavity.

The operation ends with the creation of a continent appendicostomy (Mitrofanoff principle; Fig. 3). In some cases it is possible to also carry out the Young-Dees-Leadbetter bladder neck reconstruction (Fig. 4).

30.5
Post-Operative Management

In the early post-operative period the new bladder is periodically irrigated with saline solution, until the removal of the ureteral stents which generally takes place at around the seventh post-operative day. This procedure is carried out to dilute the gastric secretions until the arrival of the urine in the bladder and its buffering effect. The vesical catheter is maintained until the fourteenth day, whereas the sovrapubic catheter is generally removed after the start of the intermittent catheterization (4–6 weeks) and after the cystourethrogram. Endoscopy of the bladder and neourethra can be performed 4–6 weeks post-operatively to evaluate their condition for catheterization.

Antibiotic therapy is suspended after 3 weeks and substituted with prophylaxis for about 3 months following surgery. Oral therapy with proton pump inhibitors is continued for some time (at least 12 months).

All patients undergo radiological and echographic checks of the new reservoir at 1 month from surgery. The complete uroradiological follow-up is carried out after 6 months. Nephrological and gastroenterological checks are carried out after surgery and then yearly. Cystoscopy is performed every 2 years for tumour surveillance.

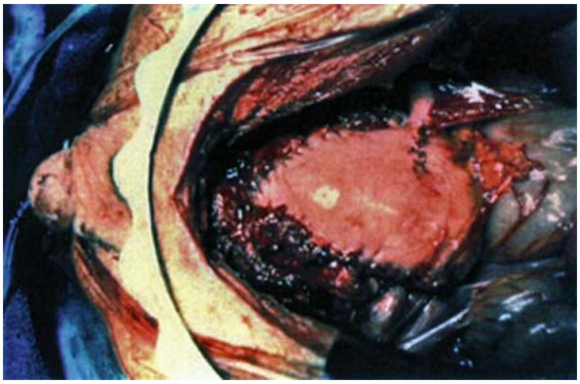

Fig. 3. Gastrocystoplasty and appendicostomy (Mitrofanoff principle)

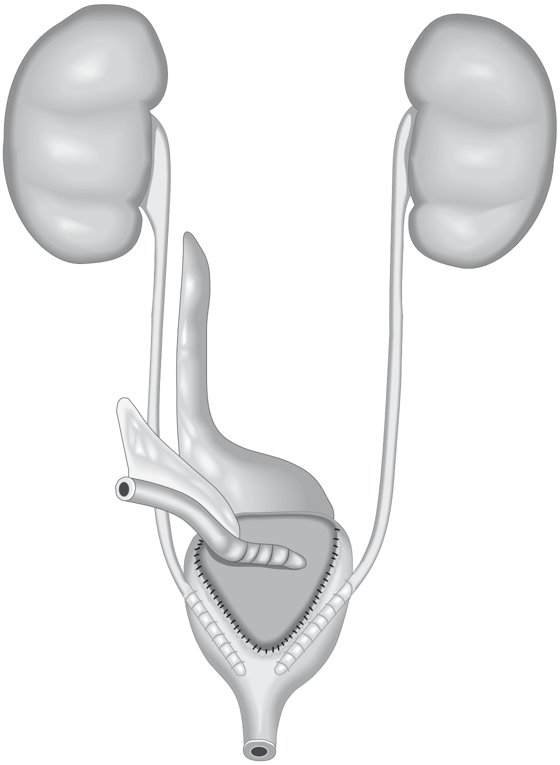

Fig. 4. Gastrocystoplasty

30.6 Complications

It is possible to have both early and late complications; the first concern the stomach (bleeding), bladder (perivesical extravasation) and reimplanted ureters (obstruction). Intestinal obstruction, spontaneous vescical perforation, haematuria and/or dysuria are late complications.

The haematuria/dysuria syndrome is a complication linked specifically to the use of the stomach for bladder augmentation. Described for the first time by Nguyen et al. [23], it has an unclear aetiopathogenesis and seems to affect patients with a reduced renal function and patients who are not completely continent [6, 24].

According to some authors, this syndrome could be secondary to the activation of some enzymes such as pepsinogen, which, secreted by the gastric cells when the urinary pH goes below 3.5, could be converted into pepsin, which could damage the urothelium of the native vesical plaque [5, 23].

An alternative explanation is given by irritation and potential ulceration, due to the action of *Helicobacter pylori*, the same pathogen responsible for gastric ulcers.

An elevated risk of developing a peptic ulcer in the defunctionalized gastric portion of the GCP has been reported [9]. The symptoms are generally intermittent and ingravescent. The severity of the symptoms range from intermittent dysuria to the rare formation of ulcers and gastric perforation. The symptoms are more evident in adult patients. Most patients undergo intermittent therapy with H2 blockers and proton pump inhibitors, vesical washing or oral therapy with sodium bicarbonate.

Notwithstanding the many advantages of GCP, it is necessary to inform patients about the possibility of a haematuria/dysuria syndrome.

Despite the many successful results reported with GCP, the complications, such as alkalosis and haematuria/dysuria syndrome, have reduced the use of the stomach for bladder augmentation during the past 5–10 years [5, 17, 25–27]. Research into the best treatment is still underway.

Presently, the use of the gastric patch in the reconstruction of the lower urinary tract is indicated for those patients with reduced renal function and metabolic acidosis, with vesical estrophy or complex syndromes, such as estrophy of the cloaca, and in those with short bowel syndrome or those who have undergone pelvic radiotherapy.

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Laparoscopic-Assisted Augmentation Ureterocystoplasty

31

Chung K. Yeung · Christoph H. Houben

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31.1
Introduction

The history of bladder augmentation goes back to the experimental approach by Tizzoni and Foggi in 1888 [41]. In 1899 the German journal “Centralblatt für Chirurgie” published two articles about the use of bowel for bladder augmentation in humans. Mikulicz [33] reported his experience with a case of bladder extrophy (also cited in [40]). Lemoine demonstrated the use of sigmoid colon in bladder augmentation in 1912 (cited in [5]). In the 1950s numerous ways were described to increase bladder capacity with segments of bowel ranging from the ileum to the sigmoid colon [10, 21]. In 1977 Adams et al. described the use of the segments of the stomach to achieve a gastrocystoplasty [1].

A segment of the intestinal tract is the most commonly used substrate to increase bladder capacity and enhance bladder compliance in children with a neurogenic bladder, a non-compliant bladder following a congenital obstructive posterior urethral membrane (COPUM) or bladder dysfunction following bladder extrophy; however, the method is associated with a considerable number of complications [20]. Post-operative adhesive bowel obstruction is seen in up to 10 % of patients [24, 39]. Various metabolic changes are associated with different bowel segments: hyperchloraemic metabolic acidosis is associated with the use of either ileum or colon [25]. Long-term evaluation of bone mineral density (BMD) in patients with ileocystoplasty – excluding the subgroup in which a low bone mineral density is part of the natural history (e.g. myelomeningocele) – revealed a reduction of BMD in more than 30% [26]. The metabolic changes may even contribute to delayed growth [28].

Hypochloraemic, hypokalaemic, and metabolic alkalosis may be observed in patients following gastrocystoplasty [23]. In addition, patients with increased acid secretion by the gastric mucosa may develop haematuria-dysuria syndrome [34]. Acidic urine may provoke external excoriations. Urinary tract infections are reduced but still common after bladder augmentation in patients who continue to require continuous intermittent catheterisation (CIC) [39]. A further complication of intestinal segments incorporated into the bladder is mucus production. Regular bladder irrigation is recommended as mucus may provoke urinary tract infections and stone formation [13, 39]. The formation of calculi, mostly struvite in composition, has been noted in 8–52% by Palmer [35; also cited in 13]. It appears that stone formation is triggered by mucus, permanent sutures/staplers, poor bladder emptying and bacteriuria, particularly in urea-splitting organisms [39]. Adenocarcinoma, possibly caused by N-nitroso compounds, develops in augmented bladders as early as 4 years after cystoplasty [4, 18, 19]. Finally, delayed spontaneous bladder perforation is seen in connection with intestinal bladder augmentation, most likely caused by chronic bowel ischaemia [11, 12, 37].

31.2
Evolution of Ureterocystoplasty

Considering the long list of potentially serious complications associated with intestinal bladder augmentation, it is not surprising that investigators are searching for alternatives. Transitional epithelium would be well suited to increase the bladder capacity without detrimental metabolic changes, increased mucus production, and a long-term risk of malignant transformation of the intestinal sphere incorporated in the bladder wall. It is a well-established observation that unilateral reflux in a bladder with high intravesical pressure may behave as a "decompression chamber" and protect the contralateral kidney. Approximately 15–20% of patients who had treatment for COPUM in the neonatal phase develop secondary to the high intravesical pressure a unilateral vesico-ureteral reflux with renal dysplasia (VURD syndrome) [29]. Eckstein and Martin were the first to take advantage of this "pop off" valve in a renal drainage system: they removed the dysplastic kidney in a 7-month-old patient and incorporated the longitudinally incised dilated renal pelvis and ureter into the bladder [17]. Two decades later, the idea was reintroduced by several groups [3, 6, 38]. A midline incision allows transperitoneal access for mobilisation of the dysplastic kidney and dilated ureter, and incorporation of the ureter into the bladder [6, 31]. An entirely extraperitoneal approach has the obvious advantage of obviating the risk of adhesive obstruction following surgery. Preservation of the integrity of the abdominal cavity is also beneficial for the safe placement of a ventriculo-peritoneal shunt and allows for peritoneal dialysis, should this become necessary [3, 16, 38, 42]. The procedure is carried out through a double incision: the flank incision allows the mobilisation of the non-functioning kidney and ureter, and the second suprapubic incision allows access to the bladder to perform the augmentation.

In the aforementioned studies the entire length of the ureter and pelvis of the non-functioning, dysplastic kidney could be used for the augmentation. Other researchers established that only approximately two-thirds of the length of a dilated ureter may be sufficient to achieve the objective of increased bladder capacity and improved bladder compliance, allowing for the preservation of the ipsilateral kidney through a trans-uretero-ureterostomy [14, 22, 27]. The procedure is done via the transperitoneal route; however, it has been proven that this kind of reconstructive surgery can be performed with two incisions in an extraperitoneal fashion: the plain between the peritoneum and the great vessels is developed to gain access to the contralateral ureter [15].

Concerns have been raised about the distal end of the ureter, as to whether it can be used in its entire length or whether its distal part should be left alone. The ureter is in the male in close proximity to the vas, and its blood supply depends on branches of the superior vesical artery [2, 42]. Churchill et al. proved that the whole length of a ureter could be safely used to be incorporated into the bladder, even after a previous reimplanation [7].

31.3
Laparoscopically Assisted Ureterocystoplasty

In a further development, bladder augmentation with native urothelium is done with laparoscopic assistance [8, 9].

31.4
Pre-Operative Patient Preparation

The patient caregiver is informed about the risk factors for the surgery. The consent should cover the risks of open and laparoscopic-assisted nephrectomy: injuries to vascular structures, bowel and intra-abdominal organs (e.g. spleen, liver, pancreas), and risk of infection/thrombo-embolic abnormalities. The procedure involves three small flank incisions for the laparoscopic ports to help mobilisation of the kidney and ureter, as well as a "Pfannenstiel" incision for the bladder augmentation and removal of the dysplastic kidney.

Routine pre-operative evaluation should cover laboratory investigations (electrolytes, renal function, complete blood cell count, urinalysis), imaging of the renal tract and studies of the urodynamics. Bowel preparation is considered mandatory should the ureteral segment for augmentation appear inadequate or should a composite reservoir be required. The patients are cross matched for 1 U of packed cells, and on the evening before surgery an enema is administered. Intravenous fluids can be considered to ensure good hydration.

31.4.1
In the Operating Room (Patient)

The well-hydrated patient is anaesthetised, is given perioperative antibiotics (cefuroxime or amicazine) and is catheterised; NG-tube drainage secures bowel decompression. The patient is placed in a lateral decubitus position exposing the appropriate flank. The flank and suprapubic area are prepared and draped with the Foley catheter maintained in the sterile field. The lower leg is flexed 30° at the knee and hip. The top leg is placed on pillows and the upper arm is supported over the patient. The operating table is flexed and the patient is strapped to maintain the position.

31.4.2
In the Operating Room (Setup)

In the operating room the surgeon and camera operator stand on one side. The first surgical assistant and the scrub nurse are with the instrument table on the other side. Behind the first surgical assistant, above shoulder height, is the primary video monitor with the CO_2 insufflator, light source and recording devices on the same stand. Behind the surgeon is the secondary monitor installed next to the electrosurgical unit. The irrigator/aspirator setup is placed at the bottom end of the table. The anaesthetist is at the head (Fig. 1).

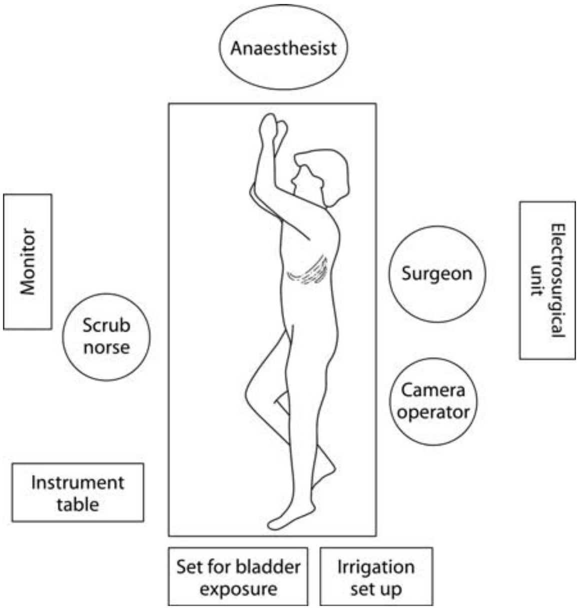

Fig. 1. Operating-room setup for laparoscopic-assisted ureterocystoplasty

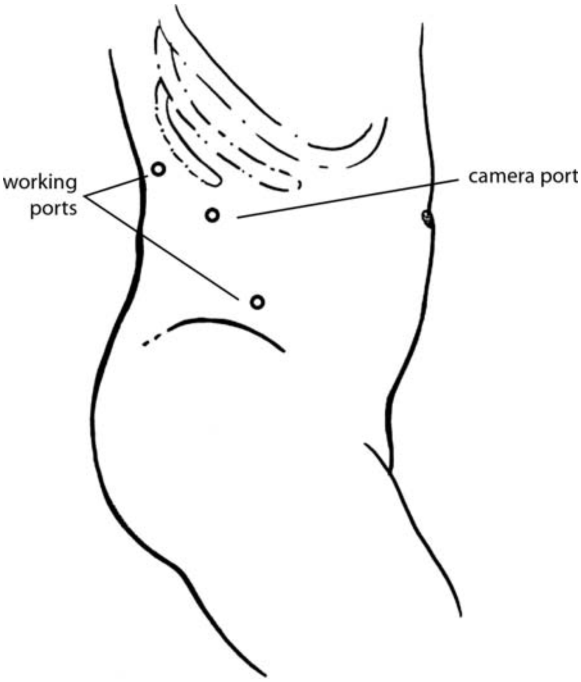

Fig. 2 . Port placement for mobilisation of kidney/ureter

31.4.3
Port Placement

The first incision is made at the tip of the twelfth rib. A "ballon", usually a size-8 glove, is inserted into the retroperitoneal space and inflated to create a working space for the instruments. Following this manoeuvre, the camera (5-mm port) is advanced and CO_2 insufflation into the retroperitoneal space is started at 12 mmHg. Two working ports for 3 mm instrumentation are inserted as illustrated in Fig. 2.

31.4.4
Operative Procedure

Gerotas fascia is incised and dissected to visualise the kidney. Retracting the upper or lower pole of the kidney should facilitate the dissection of the vessels. Once a complete window is created around the artery and vein, both vessels are clipped and divided in turn. Following the freeing of the anterior aspect of the kidney, great care is taken to preserve the blood supply to the ureter while mobilising it down to the pelvis. The dysplastic kidney and the ureter are placed in the pelvis. The laparoscopic instruments are removed, the port sites are closed and the patient is repositioned supine for the Pfannenstiel incision. The laparoscopically mobilised ureter is accessed and detached from the dysplastic kidney. The bladder is opened in a sagittal or eccentric fashion, avoiding the blood supply of branches of the superior vesical artery. The ureter is opened in its entire length along the longitudinal axis, preserving its blood supply and not detaching the distal ureter from the bladder. The ureter is folded on itself and sutured with an absorbable continuous suture. The reconfigured ureter is then incorporated into the bladder (Fig. 3). A soft rubber drain is placed besides the base of the bladder and a suprapubic catheter is placed through the old bladder wall. Then the Foley catheter is removed.

31.4.5
Post-Operative Management

The drain is removed 48–72 h after insertion, if drainage is minimal. Post-operative parenteral antibiotics are continued for 72 h. In the initial post-operative phase close monitoring of fluid and electrolyte status is mandatory. Spontaneous voiding may commence at any time, but the suprapubic catheter should be left in situ for approximately 3 weeks. A cystography should document absence of leakage before CIC is restarted, if necessary. Urodynamics are planned at around 6 months following the procedure.

31.5
Results

Results with laparoscopically assisted ureterocystoplasty are currently limited to very few publications. No serious

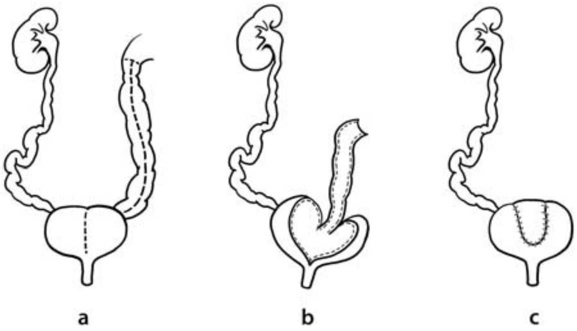

Fig. 3. Steps of ureterocystoplasty. **a** Mobilised ureter following resection of the dysplastic kidney. **b** Bladder opened in clam-like fashion with the longitudinally incised ureter. **c** Completed ureterocystoplasty

complications associated with the procedure have beeen reported [8, 9]. The overall experience with conventional and laparoscopic-assisted uerterocystoplasty is favourable [3, 14, 16, 23, 27, 31, 38, 42]. Churchill et al. reported a rare extravasation of urine in the early post-operative phase [6]. The technique of using native urothelium for augmentation is not hampered by the long list of complications and problems associated with intestinal patch augmentations; however, some concerns have been raised: A spontaneous perforation of the augmented bladder has been reported on two occasions [30, 36]. It is speculated the perforation is a result of the thin muscular backing of the ureter and the more rigid type-III collagen which is present in high levels in megaureters [32].

Extended follow-up series present mixed results. A multi-institutional review of the ureterocystoplasty concluded a need for re-augmentation in 80% of the patients with refluxing ureters and moderately to severely non-compliant systems (compliance <20 ml/cm H2O); a largely successful augmentation was observed in patients with mild non-compliance (compliance >20 ml/cm H2O) and a wide (>1.5 cm) ureteral diameter [30]. In contrast, a single-centre study reported persistent normalised compliance in 90% of the patients who had a spherically folded ureter incorporated into a small bladder [31]. Interestingly, one patient with poor compliance required a secondary augmentation.

Current experience with the method suggests that careful urodynamic assessment of potential candidates for ureteric augmentation is required; thereby patients with mild non-compliance as well as patients with a uretheral diameter >1.5 cm are most likely to benefit from the procedure.

31.6
Outlook

Ureterocystoplasty is very well suited for the triple objective of bladder augmentation: increased bladder capacity; enhanced compliance; and limited detrusor overactivity. It has a considerable advantage over the intestinal bladder cystoplasty, as it does not share the range of complications associated with this kind of augmentation. Careful selection of patients with urodynamic evaluation is mandatory. An expansion of the laparoscopically assisted ureterocystoplasty into preservation of a proximal ureter with salvageable renal function appears feasible with the expected advancement in retro-peritoneoscopic surgery.

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The Mitrofanoff Principle in Urinary Reconstruction in Children

32

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Jean Stephane Valla

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32.1
Introduction

The lower urinary tract consists of a reservoir, a conduit to the surface and a continent mechanism. The bladder and urethra with their sphincters comprise the most efficient system and should be abandoned only if they are hopelessly diseased.

Historically, three distinct phases are observed for the operations performed for urinary diversion.

From the beginning of modern surgery in the second half of the nineteenth century, the urine was diverted into the colon, with continence depending on the integrity of the anal sphincter [3, 6]. The ureterosigmoidostomy was the most commonly used technique.

The second phase of development began in 1950 with the introduction of the ileal conduit [3, 6]. The third phase, continent urinary diversion, first became practicable with the adoption of the Kock pouch for the storage of urine in 1978 [3, 10].

In 1980 Mitrofanoff described a principle to achieve urinary continence. In the original procedure, the ureter or appendix was tunnelled submucosally into the bladder and anastomosed to the right lower quadrant or umbilicus. This was used as a catheterizable channel. There are two major requirements for a catheterizable conduit: (a) to provide easy clean intermittent catheterization (CIC); and (b) to provide adequate continence [1].

The Mitrofanoff principle fulfils both of these requirements, and it is especially helpful for those children who cannot catheterize the native urethra.

32.2
Indications for Continent Urinary Diversion

As mentioned previously, the natural lower urinary tract (the bladder, the urethra and the sphincters) is incomparably better than any continent diversion, so every effort should be made to preserve it or to reconstruct it. The Mitrofanoff principle is appealing, because it provides an alternative conduit to the urethra in reconstructive bladder surgery and allows patients with sensitive, absent or traumatized urethra to perform CIC easily [10]. The Mitrofanoff principle has been applied to patients diagnosed with many conditions such as classical bladder exstrophy, cloacal exstrophy, myelodysplasia, posterior urethra valves, voiding dysfunction, vesicoureteral reflux, absence of bladder, myelomeningocele, traumatic loss of urethra, and prune-belly syndrome [9]. Indications for surgery include urinary incontinence, non-diversion and continent urinary diversion, neurogenic bladder with renal deterioration, and severe voiding dysfunction.

32.3
Surgical Technique

Mitrofanoff's name is given to the principle of burying a narrow tube within the wall of the bladder or urinary reservoir whose distal end is brought to the abdominal wall or perineum to form a catheterizable stoma suitable for intermittent catheterization (Fig. 1).

The technique is simple and familiar to all urologists who are accustomed to re-implanting ureters. Furthermore, it is a procedure that is easily learned. Several narrow tubes are available for the Mitrofanoff conduit. In the original description, the appendix was used [10]; however, even if the appendix is still present, it may be unusable in 31% of patients [2, 11].

The appendix, if present, however, remains the best choice for a Mitrofanoff conduit. It commonly admits a 12-F catheter and has a good vascular pedicle.

The wall is compliant and thin enough to allow easy submucosal implantation.

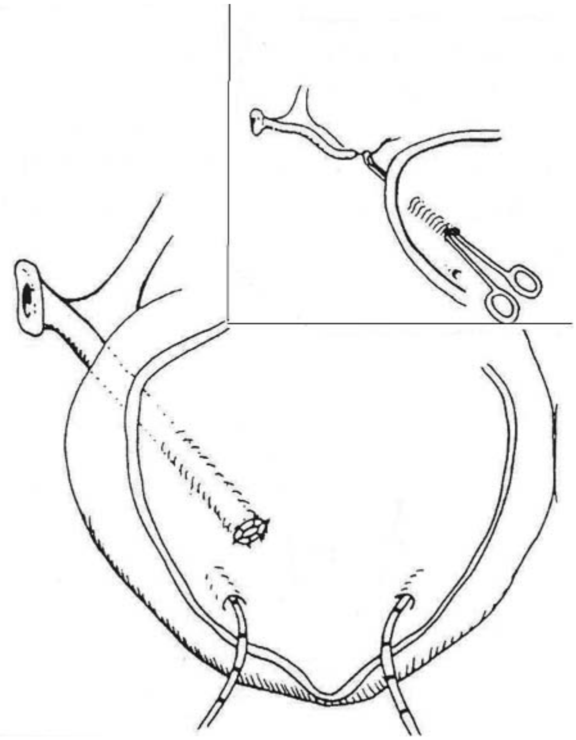

Fig. 1. Mitrofanoff's name is given to the principle of burying a narrow tube within the wall of the bladder or urinary reservoir whose distal end is brought to the abdominal wall to form a catheterizable stoma suitable for intermittent catheterization.

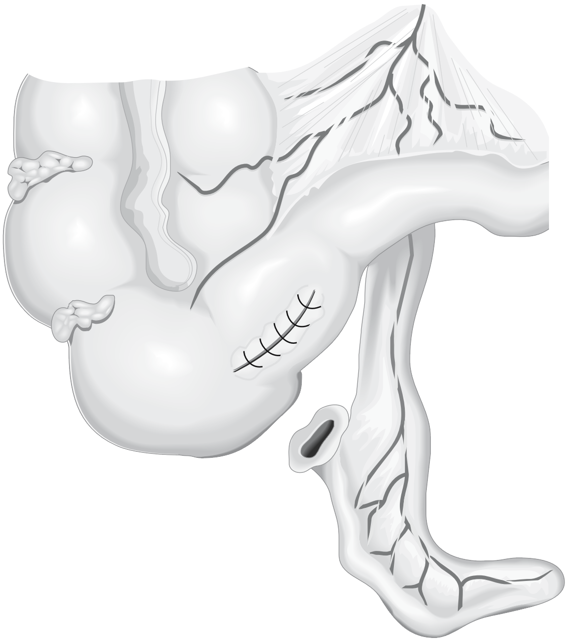

Fig. 2. The appendix is mobilized with a 3- to 4-cm cuff of cecum to allow lengthening of the conduit, should it be too short.

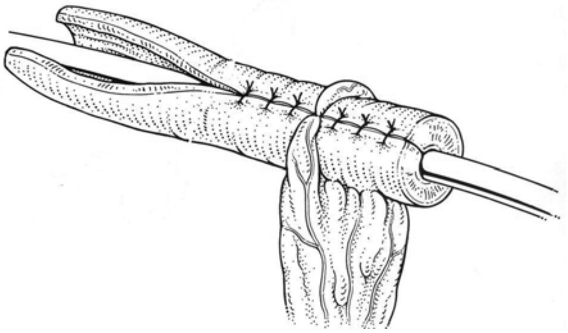

Fig. 3. If the appendix is not available, the best choice for the conduit is a segment of tailored ileum. A 2.5-cm-long ileum is isolated on a good pedicle. It is opened longitudinally and is closed transversally over a 16-F catheter with interrupted absorbable suture.

The appendix is mobilized with a 3- to 4-cm cuff of caecum to allow lengthening of the conduit, should it be too short (Fig. 2). The co-lateral supply of the caecum from the appendicular vessels is tenuous. Mobilization of the pedicle should be kept to a minimum. The distal tip is resected. If the appendix is not available, the next best choice for the conduit is a segment of tailored ileum [13, 14].

This very useful technique was originally described independently by Yang in humans [13] and by Monti et al. [12] in experimental animals.

A 2.5-cm-long ileum is isolated on a good pedicle. It is opened longitudinally, not on the antimesenteric border, but one-quarter of the way around. Having been opened longitudinally in this way, the ileum is closed transversally over a 16-F catheter with interrupted absorbable suture (Fig. 3). This produces a tube 7 cm long with a pedicle closed to one end.

The end remote from the pedicle is implanted into the bladder or into another reservoir creating a submucosal tunnel to keep continence (Fig. 4). The other end of the conduit is implanted into the abdominal wall and this edge it is used for catheterization. The ureter may be also, used but there may be some difficulty in achieving sufficient caliber with a previously normal ureter [16, 17].

Previous reports that the Fallopian tube could be used have not stood the test of time [13, 15]. The Mitrofanoff system achieves reliable continence which is maintained in long-term follow-up, for a high proportion of patients.

The pressure generated within the lumen of the conduit is two to three times higher than that within the reservoir, so that continence is preserved even when the intra-abdominal pressure is raised by straining [4, 10].

Another important step of the procedure is the selection of an appropriate site for mucocutaneous anastomosis. This choice is based on the mobility and origin of the blood supply and the type of conduit select-

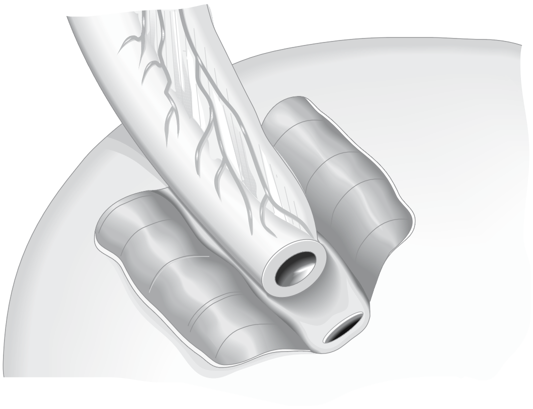

Fig. 4. The end of the appendix is implanted into the bladder creating a submucosal tunnel to keep continence.

ed, the presence of midline or umbilical hernias and/or scars, abdominal wall thickness and other stomal position [10].

In the Mitrofanoff procedure, the ureter is always brought out to a lower quadrant position, because it must transverse the peritoneum with an S-shaped curve to reach the umbilicus, which is farther away from the ureter than the skin of the lower quadrant [1, 10]. It is important to underline that to prevent the stenosis of Mitrofanoff's stoma, it is important to create an insertion V or U skin flap or a VQZ plasty.

The construction of a conduit to the umbilicus is another alternative. An umbilical stoma has three advantages. Firstly, it provides a better cosmetic appearance than constructing a conduit in the right lower quadrant [14, 16]. Psychological issues are as important as the anatomical and functional assessment of the urinary system. Secondly, it minimizes the distance of the conduit passage through the abdominal wall. Thirdly, because it provides a stomal site above the belt line, children can perform CIC independently, without taking off their clothes [14, 16]. This improves the quality of life.

The conventional approach to perform Mitrofanoff procedure is open surgery. In recent years several investigators have successfully incorporated laparoscopy into the paediatric reconstructive procedure to minimize postoperative patient morbidity and improve cosmesis [7, 8].

32.4
Complications and Long-Term Follow-up

The successful treatment of urinary and fecal neurogenic incontinence can dramatically improve the quality of life of affected children [12]. Many patients with a neurogenic bladder who undergo continent reconstruction of the urinary tract also have fecal incontinence, and successful management of both problems is important for achieving overall success in improving the quality of life. The development of the Mitrofanoff principle has been a major contribution to the current success of continent urinary tract reconstruction in children [1].

Since its introduction in 1980, the appendix has become the conduit of choice for the Mitrofanoff procedure. A constant and reliable blood supply, supple muscular wall, and adequate lumen and length contribute to its appeal [10]. It is important to underline that to prevent the stenosis of Mitrofanoff's stoma, it is important to create an insertion V or U skin flap or a VQZ plasty.

The cosmetic appearance of the abdomen can be improved by concealing the cutaneous stoma within the umbilicus [6]. Also, if open surgery seems to be the main adopted procedure to create a continent stoma according to Mitrofanoff, laparoscopy can be an useful alternative to perform it [7, 8].

Continence rates of 90–100% with the Mitrofanoff principle are reported, regardless of diagnosis, reservoir or conduit type [1, 15]. Follow-up in large numbers of children for at least 10–15 years has shown that the system s resilient [16]; however, stoma-related complications are common in continent urinary diversion.

De Ganck et al. reported a 36% stoma complication rate with a mean follow-up of 2.8 years, using appendix and the Monti tube as a conduit [5]; however, most complications were mild and easy to treat, such as stoma stenosis. In the majority of cases a simple dilatation is able to solve the stenosis of the conduit and only few cases require a revision of the stoma [5].

There is a controversy as to whether the type of channel used affects the rate of stoma-related problems. Reported incidences of catheterization problems with appendix varies between 15 and 40% according to different series [15, 16]. While the exact aetiology of the strictures in the appendiceal conduits is unknown, it seems that ischaemia, recurrent trauma, body habitus or uneven growth rates between the Mitrofanoff conduit and the abdominal wall may be factors [5, 16].

Narayanaswamy et al. published their experience with the Yang–Monti ileovesicostomy and they had considerably more catheterization problems (60%) using this procedure for urinary reconstruction compared with the other series that used appendix [13]. In that series, seven (28%) patients developed a pouch-like dilatation of the Yang–Monti conduit, creating catheterization difficulties. This problem is less common when the conduit is made with appendix.

In the non-appendicular conduits, the most frequent cause of difficulty in catheterization is related to excessive angulation of the conduit, although this is probably a technical fault caused by the excessive extravesical length of the conduit [5, 13]. We nevertheless believe the appendix to be the best choice because the complication rate is lower.

In conclusion, it seems that the Mitrofanoff principle with umbilical stoma is useful for patients who need an easily catheterizable conduit, and provides adequate continence with a good cosmetic appearance.

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Management of Constipation in Neurogenic Bladder Dysfunction

33

Agnès Liard · Fréderic Elbaz · Bruno Bachy

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33.1
Introduction

Constipation in patients with neurogenic bladder dysfunction has been disregarded for a long time. Perhaps because it does not evolve to progressive bowel function impairment, colic compliance allows long-term adaptation; however, its social impact is fundamental, and care of this condition has improved much with real effects during the past decades.

Constipation is always present in neurogenic bladder, arising from the same dysfunction. It would be more appropriate to talk about a “neurological colo-rectal” condition. Clinical presentation results in association of neurological colonic constipation (slowness, laziness and dysfunction of bowel motility) and anal incontinence by lack of innervation and weak pelvic floor. This major constipation leads to fecal impaction, which prevents leakage and permits a certain social adaptation. Evacuation of those bulky stools empties the bowel. Stool softening or infection can lead to uncontrolled soiling, which can be very unpleasant.

Furthermore, fecal impaction increases urinary incontinence, and care of sphincter impairment in those patients must be included in a common strategy. Those colo-rectal dysfunctions are constant and must always be detected at initial evaluation, although they are usually hidden behind urinary symptoms. Constipation and fecal incontinence often become evident when the urinary condition gets better; therefore, it is very important, in the first consultations of these patients, to talk about constipation and fecal continence, in order to suggest a common treatment approach to sphincters dysfunction. Curing this constipation requires a good understanding and good cooperation from children and their parents. There is no universal treatment or “miracle” medication.

33.2
Clinical Evaluation and Investigations

The evaluation of constipation is primarily clinical. A history from the parents, or from the child himself as soon as he is old enough to understand the importance of it, is fundamental. Details of the number of times stools are passed and whether they are liquid, soft, normal or hard are essential. Inquiry into nutrition is also important. Sphincter difficulties must be identified as soon as possible in order to correct them or to minimize their consequences.

The abdomen is examined for distension and fecal loading is often found in the sigmoid colon. Perineal and rectal examination complete this clinical evaluation: anal inspection, a permanent anal gaping which predicts major care difficulties; as well as anal tone and levator ani tone by digital rectal examination.

Many investigations offer poor help: standard X-rays simply confirm clinical findings. Bowel transit time of radiopaque markers is always disturbed, but analysis of this factor rarely changes treatment approach. Defecography is not effective in neurological constipation.

Electrophysiological investigations with rectal manometry, as well as volume and compliance studies, are helpful mostly in a surgical-approach strategy.

33.3
Medical Treatment

33.3.1
Diet

Hygieno-dietetic therapy and diet are very significant [1, 2], whatever the treatment approach selected. High-fibre diets make transit easier but often involve liquid stools, which lead to uncontrolled soiling. Patients generally avoid these diets and instead prefer for low-fibre diets.

In time, the child will learn to manage his diet by himself. In the first years, diapers are easily accepted, but in time they become less acceptable to the parents and progressively less acceptable to the child. This is more obvious when the child approaches puberty, when self-perception becomes very important, and it is frequently observed that the teenager manages his own transit better. It remains important to talk about transit difficulties and to evaluate the child's feelings in this regard. After several years, a more intensive treatment can be proposed, if necessary.

Some patients adhere to a low-fibre diet to harden their stools, which facilitates their continence. Some patients also take medications, such as Loperamide, to retard bowel movement. In those cases, stool evacuation is often manual.

33.3.2
Laxatives

Laxatives, such as polyethylene glycol, are well tolerated over long-term use, even in young infants [3, 4], but they cause flooding diarrhoea with soiling, which is embarrassing in school-age children.

33.3.3
Manual Evacuation

Manual evacuation is a common technique widely used in patients with neurological constipation. It is used in association with low-fibre diet promoting hard stools. Manual evacuation must be performed on a daily basis to avoid uncontrolled leakage. It does not obviate soiling or flooding diarrhoea which accompanies fecal impaction. Patients, particularly those with orthopaedic difficulties, often depend completely on their caregivers.

33.3.4
Suppositories and Enemas

Medications such as Eductyl, Microlax and Normacol permit rectal vacuity, but only if the medication can stay in contact with the stools long enough, which is not evident in patients with associated anal incontinence.

33.3.5
Enema Continence Catheter or "Colic Wash-Out" Technique

To improve duration of contact, enema continence catheter, or "colic wash-out", was introduced 20 years ago [5]. This enema is given with a long catheter, which improves efficiency. The catheter is introduced into the rectum and a balloon is inflated with air until a waterproof state is reached. Enema is given through the catheter and left in place for 10–15 min, then the balloon is deflated and the catheter is extracted to permit stool evacuation. Abdominal massages can be performed at the same time. This procedure is efficient, but long-term acceptance is poor and dependence on the caregiver(s) remains necessary.

33.3.6
Biofeedback Re-education

Biofeedback re-education has its role when the child still has rectal feeling and stool evacuation needs attention. It can be effective in patients with anorectal malformations with a substitute anal and rectal innervation. It can be tried in patients with spina bifida, but results vary and are better if spinal interruption is lower, in L2. This technique, proposed on a limited basis, helps children to understand the rectal feeling but does not allow the reinforcement of an insufficient sphincter [6–8].

33.3.7
Anal Plugs

Anal plugs improve anal continence during the day, but their use is complicated in children with significant physical difficulties or those dependent on other people. Anal plugs are useful in association with an evacuation technique to reduce soiling.

33.4
Surgical Treatments

33.4.1
Antegrade Continence Enema

The principle of antegrade continence enema is body-friendly, since bowel irrigation is performed in the right way (Fig. 1). The regular emptying of the colon obviates unpleasant fecal incontinence. The antegrade enema requires a surgical procedure.

33.4.2
Malone Original Procedure

The point of the Malone procedure is to directly give the enema into the caecum and to "wash" the colon forward [9]. Malone has proposed a very simple technique (Fig. 2): the appendicostomy, which consists of placing the appendix turned around between the abdominal wall and the caecum. The surgical procedure is simple: by a horizontal incision in the right iliac fossa, the appendix is located and sectioned at its base, keeping its vessels intact. The appendix is then turned around and inserted in a taenia of the caecum. Caecal implantation of the appendix is performed as an antireflux procedure, laying down in a taenia. The proximal end of the appendix is pulled through the abdominal wall and sutured

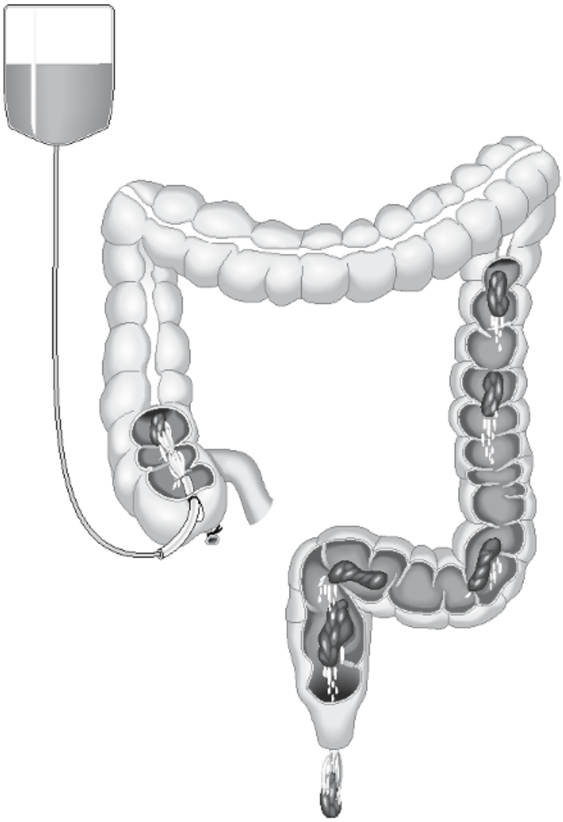

Fig. 1. Principle of antegrade continence enema

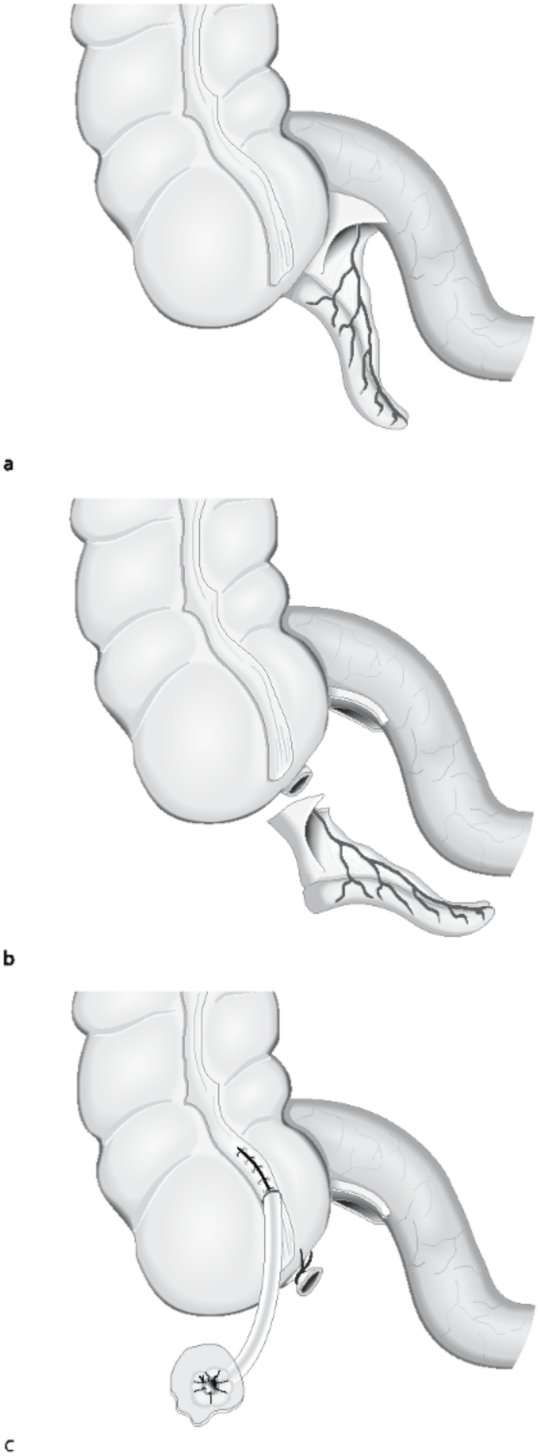

Fig. 2. a–c The MALONE original procedure

to the skin. The appendix direction must be as straight as possible to facilitate catheter insertion. If the appendix is short, the caecum can be fixed to the anterior abdominal wall. Appendicostomy is fixed to the skin with an absorbable interrupted suture. A plastic procedure is often required to avoid secondary stenosis: a "V" skin flap is inserted into a longitudinal incision at the end of the appendix.

A balloon catheter (Foley catheter 8 or 10) is left in place for 14 days, until complete cicatrization occurs. The child is discharged home on the fourth or fifth day, as soon as regular transit returns. The first and second enema are performed on the eighth and eleventh days in the hospital ambulatory department, permitting the child and his family to learn the enema procedure. On the fourteenth day, the Foley catheter is taken off. Learning stoma catheterization is fast, and the child can perform rapidly his own antegrade enema.

Multiple protocols are possible. They are exposed to the child and his family, who test them and chose the most appropriate one. It can be a significant enema with 3 l of water twice a week, or a smaller one with 500 ml of water every 2 days. The duration of each enema is about 45 min. The child sits comfortably on the toilet and the enema is connected. The parents must not forget to add a teaspoon of salt to a litre of water to avoid hyponatraemia, which can lead to headache due to water movement in the colon caused by hyperosmolarity. (The ideal enema would include an iso-osmolar solution such as PEG.) Water resorption can be useful to stimulate a hyperdiuresis, which is, in turn, useful to rinse, for example, an enterocystoplasty.

At home, it is advisable to use tap water (without a home softening system) with a teaspoon of salt per litre [10]. This allows an isotonic solution which diminishes water resorption. Children prefer to perform enemas in the evening, because of eventual headache and fatigue, frequently despite these precautions.

This type of antegrade enema gives total autonomy to the patient, even with significant orthopaedic difficulties. (Stoma must be placed in an accessible way for seated patients or patients in wheelchairs.)

Stoma is mostly placed in the right iliac fossa. It is very discreet, as a simple "star" scar sometimes, with a little mucosa visible, hidden under the underwear. This kind of stoma allows regular sports practice, and even bathing. Appendicostomy can also be placed in the umbilicus, where it becomes completely invisible. This procedure is not advisable in females because of possible catheterization troubles during pregnancy. Young children do not accept easily this site because of the psychological implications of the umbilicus in toddlers [11, 12].

The Malone procedure can be performed in young children, as soon as 2 years of age. In fact, it is frequently performed around age 5 years to permit school integration by minimizing fecal incontinence and facilitating everyday care.

This procedure can be performed simultaneously with urological reconstruction. In this case, appendix is reserved for the caecostomy and a Monti tube is used for the continent cystostomy, if needed.

Some complications can occur, necessitating surgical reintervention in some cases: orificial stenosis (diminished by the VQZ technique) and necrosis of the appendix, leading to a replacement of the appendix by a Monti tube [13, 14].

The Malone procedure provides a continent device without leakage from the skin opening. Anal leakage can be prevented by a prolonged seated station following the enema to allow complete evacuation of the solution.

Surgical modifications of the original technique have been described:

1. In situ appendix: in some cases the appendix can be turned inside out and buried into the caecal wall, allowing easy catheterization [15].
2. The Monti–Malone procedure: use of a Monti ileal tube inserted with an antireflux technique [14]. When the abdominal wall is thick, the Monti procedure is interesting because two tubes can be used, one at the end of the other, to increase possible length. Ileal use is simple and gives results as good as the appendix [16].

33.4.3
Alternative Solutions to Malone Procedure

33.4.3.1
Sigmoidostomy

The objective of sigmoidostomy is to irrigate the terminal part of the colon. On the same basis, a Monti colonic tube is placed on the sigmoid or the left colon with an antireflux procedure, the upper end being sutured to the skin. This sigmoid tube is placed preferably at the same time as the enterocystoplasty using the sigmoid colon [17–19].

This technique allows smaller and quicker enemas. Those enemas are less painful and less stool impaction occurs. Enemas are more frequent, every day or every 2 days, using smaller amounts of solution (250–500 ml). The results as reported to be as good as those with the Malone procedure.

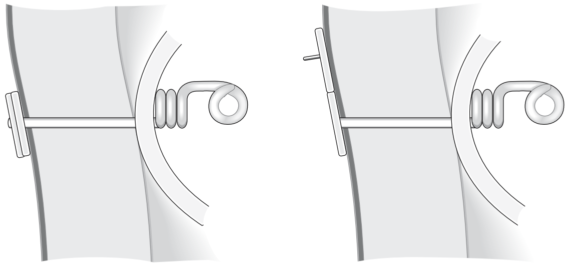

Fig. 3. Chait trapdoor cecostomy catheter

33.4.3.2
Cecostomy Button or Chait Trapdoor Cecostomy Catheter

Chait trapdoor cecostomy catheter is an appealing replacement procedure to appendicostomy (Fig 3). The device is placed percutaneously [20–22], under ultrasound control or, preferably under laparoscopy, which ensures better placement. Replacement of the catheter is easy using a simple leader. Several device sizes are available depending on the child's weight. The catheter is secured in the caecum using a pigtail end. This procedure is simple but leaves in place a visible button in the right iliac fossa.

33.4.4
Anal Sphincter Reconstruction

33.4.4.1
Dynamic Gracyloplasty

Gracyloplasty is an old technique used to improve results in anorectal malformations. Its results have been disappointing, but a recent "dynamization" possibility has improved its potential. Dynamic gracyloplasty uses the gracilis muscle removed from the lap and placed around the anal sphincter (Fig. 4) [23, 24]. It is then stimulated by an electric stimulator inserted under the abdominal skin. This stimulation allows muscle contraction and closure of the anal sphincter. To stop the stimulation a magnet is approached from the generator which interrupts the stimulation and allows rectal emptying. This surgery is underused in neurogenic fecal incontinence. It is used mostly in patients surgically treated for rectal cancer. In children, it presents the issue of placing a foreign body for a long time. Furthermore, it does not suppress the necessity of enema to evacuate stools in neurogenic constipation.

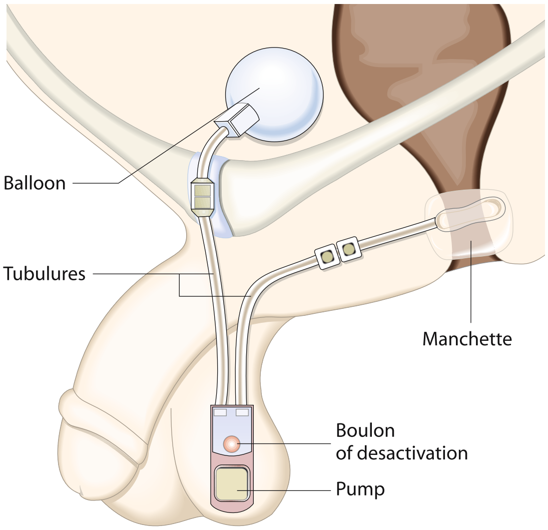

Fig. 4. Artificial anal sphincter

33.4.4.2
Artificial Anal Sphincter

Artificial anal sphincter is a procedure performed in adults [25]. Complications are frequent with anal mucosal erosion and sphincter expulsion. This technique also requires enema in neurogenic constipation and does not yield much benefit. Dependence on caregivers remains the same. Long-term tolerance is still a problem in children.

33.4.5
Terminal Colostomy

Terminal colostomy has been widely used in patients with neurological constipation. It should not be considered presently. It might be reserved eventually for patients with profound mental disabilities, to facilitate everyday nursing.

33.4.6
Sacral Nerve Neuromodulation

Sacral nerve neuromodulation is used to treat urinary incontinence. It also improves constipation. This technique has never been used alone to treat constipation and anal incontinence in children. It has been described in adults [26].

Anal incontinence and constipation are still underestimated in the treatment of children with neurological bladder dysfunction. Healing the constipation improves bladder voiding, quality of life and social development of these patients. Treatment of constipation is widely dominated by antegrade enemas using the Malone procedure.

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The Antegrade Continence Enema Procedure: Long-Term Results

34

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34.1
Introduction

34.1.1
Development

The antegrade continence enema (ACE) procedure was born out of a paradox: patients with neuropathic bladder were being subjected to major bladder reconstructive surgery, but were unable to enjoy the full benefit of their newfound urinary continence, as they continued to suffer from faecal incontinence. This was despite concerted conservative and medical management aiming to achieve regular colonic emptying. Such strategies ranged from dietary modification, toileting schedules, and abdominal or back massage, through laxatives, suppositories, and digital evacuation, to enemata and retrograde bowel washouts with a continence catheter. For patients with myelomeningocoele, persistent faecal incontinence has been shown to be a considerable problem, with one study reporting an incidence in excess of 50% [36]. Similarly, as many as 50% patients born with an anorectal malformation have long-term faecal incontinence. A comparable proportion of these also have a neuropathic bladder, many requiring corrective lower urinary tract surgery [3]. Consequently, these patients must be evaluated in a holistic way, and their urinary and faecal disabilities should be considered and treated in tandem. The development of the ACE [35], as an alternative to a last-resort colostomy, was the other side of the coin to bladder reconstruction.

The ACE procedure simply brought together three well-established surgical fundamentals:

1. Complete colonic emptying can induce faecal continence [46].
2. Complete colonic emptying can be produced by antegrade colonic irrigation [41].
3. The Mitrofanoff principle of a continent intermittently catheterisable abdominal stoma and conduit [38].

The ACE procedure, therefore, afforded these patients continent catheterisable access to their proximal colon for delivery of antegrade washouts, which provoked colonic emptying and thus faecal continence.

The technique has since also been applied to both children and adults with other causes of neuropathic bowel (e.g. sacral agenesis, and spinal and pelvic trauma, tumour or surgery) and idiopathic slow-transit constipation, as well as to children with Hirschsprung's disease and refractory chronic constipation.

Compared with rectally administered washouts, the abdominal stoma of the ACE procedure offers the possibility of independence for the patient. The advent of the ACE has also permitted reversal of a long-term colostomy in some patients [50].

34.1.2
Surgical Techniques

Pre-operative bowel preparation and broad-spectrum prophylactic antibiotics are administered. Latex avoidance is practised in patients with spina bifida.

The original operative descriptions of the ACE procedure involved amputation of the appendix from the caecum, before reversing it and reimplanting it back into a caecal submucosal tunnel in order to create a continence mechanism [33, 35] (see Figs. 1–3). The technique has now been refined in various ways.

If the appendix is being used as a conduit to the caecum, it is now no longer disconnected. Instead, it is simply folded into a submucosal tunnel on the caecum and a valvular caecal wrap is performed over it, the so-called in-situ appendix [19, 20].

Tacking the caecum to the inside of the anterior abdominal wall helps reduce tension on the conduit and may make subsequent catheterisation easier [19].

When a simultaneous Mitrofanoff conduit is required there are now several options. A long appendix can be split (Fig. 4), with the distal end serving as the Mitrofanoff and the proximal in-situ appendix as the ACE [19, 25]. If the appendix is absent, or being used as a urinary channel, a Yang-Monti detubularised, transversely retubularised conduit can be constructed [39, 57]. Alternatively, a "gastrostomy" tube or button may be placed at open operation. Good medium-term results have also been demonstrated with a caecal flap neo-appendix [6], but in the Southampton experience these flaps are associated with much more morbidity such as ischaemia, stenosis, and incontinence. A gastric tube is another possibility, but skin excoriation can be a major problem.

In severely constipated individuals, washouts via a caecal ACE can take an inordinately long time to act; therefore, a further adaptation of the ACE technique has been to site the stoma on the left side of the colon using a Yang-Monti conduit [30]. According to its advocates, theoretical advantages include gravity-assisted evacuation along a shorter route, with quicker and more predictable timing, and avoidance of the right hemi-colon which is highly compliant, highly absorptive, and which may be particularly responsible for slow transit [10]. This seems to be supported by early data suggesting reduced washout volumes, less pain, and shorter toileting times when compared with various series using a conventional right-sided ACE [10, 30].

For patients whose appendix is known pre-operatively to be unavailable, a minimally invasive technique for placing a caecostomy tube under fluoroscopic guidance has been conceived [8]. The enemata are then inserted down the tube and, after the tract has matured, the tube can be replaced with a caecostomy button device. Initial results suggest that this technique may offer a viable alternative to a formal catheterisable conduit [5, 7]; however, children often dislike wearing a permanent appliance like a button device or tube.

Exponents of the advantages of minimally invasive surgery have added the laparoscopic technique to the variety of approaches available for the formation of an ACE channel (see attached video). In most cases, the technically difficult creation of a continence mechanism is omitted, with little or no increased rate of leakage from the stoma. Since some of the port sites can be incorporated into the ACE stoma or hidden in the umbilicus, the cosmetic result is usually excellent, with a functional outcome comparable to that of the open procedure [52, 53]. The reduction in adhesion formation may also be advantageous, not least since some of this population may require later urinary tract reconstruction. Even synchronous bladder reconstruction can be achieved with laparoscopic assistance, producing superior cosmesis without compromising the functional response [9, 52].

The principles of endoscopic intervention and the left-sided ACE have been combined in recent years. A trans-abdominal colostomy tube is inserted into the distal descending colon under colonoscopic vision, in the manner of a percutaneous endoscopic gastrostomy (PEG). Washouts can be administered via this so-called percutaneous endoscopic colostomy (PEC) the next day. Following maturation of the tract, the patient can opt to either keep the tube, exchange it for a button, or have a formal conduit created, already armed with first-hand knowledge on the advantages and disadvantages of the ACE.

A surprisingly low stomal leak rate is seen with both the percutaneous radiological and laparoscopic ACE techniques, neither of which incorporate any continence mechanism. In the latter case this is thought to be due to an inherent valve system created by the length of the appendix and coaptation of its mucosa [52]. This finding suggests that such a continence manoeuvre may not be entirely necessary in the open approach [14], and some authors now advocate that the appendix is simply sutured to the anterior abdominal wall after its tip has been amputated.

34.1.3
Washout

The solution used to effect the antegrade washout typically has up to three constituents:

1. Water: usually at a volume of up to 20 ml kg^{-1} body weight.
2. Salt: provided as normal saline solution, or this can be approximated by adding 1.5 level teaspoons (7.5 ml or 150 mmol) of table-salt per 1000 ml tap water. In order to avoid the dangers of hypernatraemia [44], some centres deliberately omit the salt component and have not encountered serious hyponatraemia.
3. Laxative: phosphate, sodium picosulphate, sodium citrate, bisacodyl, polyethylene glycol, and others have been successfully employed; however, some units do not add a laxative at all, since serious side effects can occasionally occur.

It is important to appreciate that there is no universally applicable ideal solution, so there may be a need to experiment with the volume, composition, and timing of the washout for a while after the operation. Indeed, it can take more than a year of such “fine tuning” to produce reliable continence [13, 17]. In some patients this protracted improvement may be due to gradual decompression of a colon that was chronically dilated before the ACE procedure.

The solution is warmed to body temperature, facilitated by use of a drainage bag that incorporates a thermometer. A tubing set connects this bag to the catheter or button device, and filling is achieved by gravity, or syringe bolus [16], at the maximum tolerated rate, with the patient sitting on the toilet.

Depending on the laxative and volume of water used, the onset of action of the washout can be within 5 min, and is usually complete after somewhere between 20 min and 1 h [13]. Some patients find that this time passes more quickly with the help of a cushioned toilet seat, and a portable desk for homework or games [45, 58].

The interval between washouts is determined by the minimum time before incontinence or constipation recur after each enema.

34.2
Long-Term Results

34.2.1
Success Rates

During the 15 years since the publication of the ACE technique, many centres have released their data, incorporating more than 1000 children. Comparison is hindered by variations in the definition of “success” but, on average, around 80% subjects appear to have achieved complete faecal continence or suffer only occasional soiling [2, 9, 11, 14–16, 19, 22, 24, 27, 34, 43, 48–50, 58].

One early report suggested that wheelchair-bound children with myelomeningocoele had a lower continence rate after an ACE procedure than ambulant children [47]; however, this has not been reproduced by the weight of later literature, with several reports suggesting such children may actually preferentially benefit!

The ACE has also been beneficial in the treatment of chronic constipation and faecal incontinence in adults [21, 28, 55]. One small series of adults with neuropathic bowel showed statistically significant improvements in continence and toileting times, and a high rate of patient satisfaction at a minimum follow-up of 4 years [51]; however, a study in chronically constipated adults suggests that the long-term results in this older population are not as good as in comparable children, with approximately 50% rather than 80% success, and the majority requiring revisional surgery [29]. Nonetheless, this report’s authors still considered the ACE procedure an attractive alternative to colostomy or colectomy, and it does not preclude either being performed later in cases of ACE failure.

Data from several series of simultaneous combined ACE procedure and bladder reconstruction, including the Mitrofanoff procedure, suggest double continence rates of up to 95% [2, 4, 9, 11, 19, 40, 42, 54]; therefore, current evidence requires that a synchronous ACE procedure should always be contemplated when a patient with faecal incontinence is submitted to bladder reconstruction.

One recent study comparing a caecostomy button with a formal ACE in children with refractory idiopathic constipation showed no statistically significant difference in continence rates at a mean follow-up of 18 months, although the former group did encounter significantly more minor complications [5].

A number of papers in the literature now demonstrate significant objective improvements in quality of life after the ACE procedure [1, 2, 47]. One such study suggested that approximately 90% of children with neuropathic bowel report the highest possible level of satisfaction following the ACE procedure, associated with major improvements in continence, social confidence, and hygiene [58].

A recent report demonstrated for the first time that an ACE conduit was sufficiently robust to function normally during and after an uncomplicated pregnancy and vaginal delivery of a baby of average birth weight, 13 months after the ACE procedure had been performed [56].

34.2.2
Complications and Problems

34.2.2.1
General Complications

As with many intestinal procedures, recognised complications include wound infection, anastomotic leak, and small bowel obstruction secondary to either adhesions or internal herniation.

Rare cases of infection and failure of associated ventriculo-peritoneal shunts have been described [18, 24]. Similarly, a previously implanted artificial urinary sphincter is known to have become infected following an ACE procedure, and required explantation [22].

Since many of the catchment population have reduced mobility, pressure sores can also ensue, either immediately after ACE surgery [17], or due to prolonged sitting on a hard toilet seat [18].

34.2.2.2
Stomal Complications

The most frequent complication experienced in all continent catheterisable conduits is stomal stenosis, affecting approximately 30% of patients [14]. It is thought that this may relate to the relatively fragile blood supply of the appendix, which could explain why older patients suffer more stomal stenosis [29]; however, there is no statistically significant difference in the incidence of stomal stenosis when an alternative, better vascularised, conduit is used, for example a tapered ileal segment [50]. In another recent comparative study, there was no significant difference in the rate of stomal complications, whether the conduit was constructed from appendix, Yang-Monti ileal segment (mean follow-up of 59 months), or caecal flap [6]. Another group's data confirm this, with a mean follow-up of 2.8 years [4].

Some authors have suggested that the in-situ ACE protects against stomal stenosis by preserving the caecal component of the appendiceal blood supply, and they offer results that would support this theory [24].

It appears that stomal stenosis is less common when a circular muco-cutaneous anastomosis is avoided with, for example, a VQZ flap [40], or incorporating a U-flap that can also accommodate a port during a laparoscopic ACE [9]. Both of these techniques also produce a superior cosmetic appearance, as well as protecting the skin and clothing from mucous and blood.

Stomal stenosis may also be reduced by daily catheterisation of the ACE stoma in those patients fortunate enough not to have to perform daily antegrade washouts.

When established, stomal stenosis is treated initially by dilatation, often leaving an indwelling Foley catheter in the conduit for several weeks afterwards, or a ("gastrostomy") button device in the longer-term; however, inadvertent removal of these with the balloon still inflated can jeopardise the channel's continence mechanism. This is not a risk with the recently developed short silicone "ACE stopper" (Medicina, Adlington, Lancashire, UK, see Fig. 5), which has been proven useful in preventing stenosis, whether after the initial ACE or a subsequent stomal dilatation or revision. Formal revision of the stoma at skin level may be needed in recurrent cases of stomal stenosis, seen in about one-third of the initial 30%.

In the absence of stomal stenosis, some patients have trouble accessing the stoma due to its position. This is a particular hazard in those who are wheelchair-bound and have a marked kyphoscoliosis or an obese anterior abdominal wall. Placement of the ACE stoma at the umbilicus, where possible, may overcome this issue, as well as providing an excellent cosmetic result. Furthermore, adequate manual dexterity is an essential selection criterion for a potential patient who wishes to achieve independence following an ACE.

In approximately 5% patients, the stoma can prolapse. Again this is less frequently seen when a stomal skin flap has been used [4]. It often requires revision of the stoma [15].

34.2.2.3
Conduit Complications

Catheterisation difficulties are also encountered due to narrowing or kinking of the conduit itself; the former is seen more frequently in tapered ileal segments, and the latter where a double Yang-Monti channel is necessary to achieve adequate length. Ultimately, such difficulties can predispose to perforation of the conduit or the caecum [47]. These problems can largely be prevented by locating the stoma and mobilising the recipient bowel so that they are as close together as possible, with no "free" intra-peritoneal conduit.

Occasionally, necrosis of the conduit is seen [13, 19], but this appears to be less likely with the in-situ appendix.

Conversely, the continence mechanism of the ACE may become incompetent, resulting in loss of flatus or stool from the stoma. This may resolve spontaneously, even after several months [17]. If not, it may be improved by endoscopic peri-conduit injection of a bulking agent, but usually re-do plication of the abdominal end of the conduit becomes unavoidable.

Appendicitis, presenting as a subcutaneous abscess around a suppurative appendiceal conduit, has been described in one patient who had previously discontinued using the ACE stoma [32]. The authors postulated that stenosis of the disused stoma had allowed the appendix to return to its original blind-ending state, at risk of the luminal obstruction that can progress to appendicitis. They therefore advocated continued catheterisation or formal excision of any unused ACE stoma; however, there are many patients around the world with a redundant ACE, so presumably the number needed to treat to prevent one case of appendicitis would be quite high.

34.2.2.4
Caecal Complications

Rarely, the bowel may evolve around the ACE conduit [23]. Such cases of caecal or colonic necrosis can occur after a laparoscopic ACE [52] and whether the ACE is sited in the right lower quadrant or the umbilicus [26], and even after routine caecal suture fixation during the ACE procedure [26].

The latter authors postulated that regular advancement of the ACE catheter too far meant that the caecum was not adequately lavaged, leading to gradual development of a caecal faecaloma, whose weight stretched the conduit, leaving a potential space for volvulus (or indeed for internal herniation).

A high index of suspicion of the need for laparotomy is warranted in any patient with a previous ACE procedure who presents acutely with difficulty in catheterisation of the ACE stoma, abdominal pain, bowel obstruction, peritonism, or shock.

Interestingly, one victim of caecal volvulus, who required resection of the ACE conduit, later opted to undergo a replacement ACE procedure (this time using a flap into the transverse colon), which suggests he had enjoyed significant benefit from the ACE washouts [26].

34.2.2.5
Washout Complications

The washout solution itself has the potential to cause life-threatening or fatal electrolyte imbalance, particularly in young children, in the presence of chronic colonic dilatation or obstruction, or in renal insufficiency [44]. The following recommendations are especially pertinent:

1. Phosphate should not be re-administered until the previous dose has been evacuated, because of the dangers of phosphate toxicity [12].
2. Patients should be warned to stop washouts during any diarrhoeal or dehydrating illness, particularly if phosphate (which also has a high sodium content) is used, due to the risk of severe sodium disturbance and phosphate toxicity [44].
3. Patients who have difficulty preparing the washout accurately should be offered a proprietary solution instead [22, 44].
4. Those centres that advocate tap water (rather than saline) should routinely advise their patients to avoid filtered water, which has a much lower salt concentration than tap water and can precipitate symptomatic hyponatraemia.
5. Electrolyte imbalance should be excluded in any patient presenting with unexplained symptoms such as lethargy, vomiting or seizures [18, 44].
6. Autonomic dysreflexia should be anticipated in patients with a high spinal neurological level [18]. On the other hand, elimination of faecal impaction by the ACE procedure may actually cure autonomic dysreflexia [51].

Washout failure (minimal rectal evacuation within 2 h of the enema) can occur in cases of faecal impaction, which may be helped by prior administration of an oil enema via the ACE [13]. This can also be a useful rescue remedy for cases of later intermittent impaction. Washout failure is also seen in some patients with Hirschsprung's disease and anorectal malformation, so rectal examination, to exclude anatomical obstruction, is recommended at the time of the ACE operation. Delayed action of the washout can tax the cooperation of any child, and may also present bathroom access problems for other family members [18].

Conversely, rectal leakage persisting for several hours after lavage is common initially, and may necessitate protective pads. It usually responds to a reduction in the volume of the washout along with an increase in the laxative, or may improve spontaneously [13].

Pain and/or vomiting on irrigation in the first few months is experienced by about half of the patients, who may benefit from a change of the laxative, or a reduction in the dose of laxative or lavage volume used [13]. If this does not settle with time, anti-spasmodic medication, such as mebeverine, given per ACE before a washout, may help [13].

It remains to be seen whether long-term lavage may have deleterious effects on, for instance, the ileo-caecal valve or colonic mucosa [18].

34.2.2.6
Psychological Considerations

Most series reveal a rate of non-compliance leading to abandonment of the ACE stoma of approximately 10–20%. As expected, this is more prevalent in those patients experiencing any of the complications mentioned above, particularly faecal incontinence either per ACE stoma or per rectum, or an unsightly stoma. Frustratingly, though, it can also occur in a patient who appears to the surgeon to have had an excellent outcome (reliable continence and a cosmetically acceptable stoma). Nonetheless, it is encountered more frequently in those who find it difficult to adjust to the permanent abdominal stoma, the imposition of a strict and often prolonged toileting schedule, and the abdominal pain that may accompany the washout. Clearly, this explains the poor results in children under the age of 5 years [13]. It has been noted that patients with idiopathic constipation also have a higher rate of attrition of their ACE stoma, perhaps indicating a common psychological factor.

When enquired of, some patients describe a grieving reaction following the ACE procedure, thought to be due to the impact on body image (particularly when an umbilical stoma is created in a young child) and reinforcement of the underlying disability [2]. Most of them recover from this as they adapt to life with an ACE, but in those who experience complications or have a pre-operative psychological condition, these feelings may progress to frank depression. Some centres, therefore, advocate routine involvement of a psychologist in all cases undergoing an ACE procedure [2, 45].

This all serves to reinforce the priority of fastidious patient selection, ensuring sufficient motivation on the part of the patient and carers, in the face of detailed information about the potential complications and im-positions. In one recent study, some patients and families who had undergone an ACE procedure reported surprise at the daily time commitment, the tendency to abdominal pain and intermittent constipation, and the long delay before an effective maintenance washout regimen was achieved; hence, the importance of adequate pre-operative education [58]. Some units offer a dummy trial pre-operatively to illustrate the impact of the ACE on family life [45]. The essential supporting role of a dedicated continence and stoma nurse–specialist both before and after an ACE procedure cannot be over-emphasised either. This will enable, for instance, the washout regimen to be adapted to each patient's response, and families to be encouraged to persevere through the "teething problems".

On the other hand, elimination of faecal incontinence and impaction is assumed to bring real psychological benefits [16]. Certainly, there is a significant correlation between the degree of continence post-operatively and patient satisfaction [15].

34.3
Recommendations

The variety of different approaches to the ACE procedure which are available in 2006 must therefore be tailored to an individual patient's needs.

If only an isolated ACE is necessary, the advantages of minimally invasive surgery offset the marginally increased risk of stomal leakage. The laparoscopic technique is the procedure of choice for caecal placement; however, in a severely constipated patient, when left-sided placement is preferable, a percutaneous endoscopic colostomy (PEC) seems best.

If the patient requires a synchronous bladder reconstruction a formal ACE conduit is created using the in-situ appendix in the caecum, or a left-sided Yang-Monti-ACE if constipation is a severe problem.

If abandonment of a caecal ACE is threatened because of an inadequate or delayed response to washouts (washout failure), the situation can often be salvaged by conversion to a left-sided ACE [31].

34.4
Conclusion

A reproducible success rate of approximately 80% is described in most series following the ACE procedure, and this appears to be sustained in longer-term reports. When performed simultaneously with urological reconstruction, such as a Mitrofanoff procedure, double continence can be delivered to the vast majority of patients.

As a result, the lives of countless patients and their caregivers have been transformed over the last 15 years; however, there is a significant morbidity associated with the technique. While most difficulties are surmountable, or abate with time, a few are potentially life-threatening. These problems should be viewed from the perspective of patients and caregivers who may have endured many years of the debilitating physical, emotional, and social effects of constipation and faecal incontinence, and their many unpleasant treatments [58].

Recent and future technical developments may continue to ameliorate the risks of the procedure. A better understanding now exists of the pre-operative predictors of ACE success and failure. Certainly, success is more likely in non-obese patients with neuropathic bowel or an anorectal malformation, who are over 5 years old and are strongly motivated to become faecally continent [13, 37]. Nonetheless, there remains a consistent cohort of patients who, for a variety of reasons, feel unable to comply with all that the ACE demands.

Overall, a realistic expectation would be for significant improvement rather than a perfect outcome [58]; therefore, the ACE procedure should be reserved as a "penultimate resort" (before a last-resort colostomy), only to be offered once the gamut of medical management has been exhausted.

Detailed counselling pre-operatively and the day-to-day support post-operatively of a committed nurse specialist are mandatory.

It is hoped that continued objective feedback from patients and caregivers will produce further refinements in patient selection and education [58]. This can only lead to a better outcome for all.

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Neurosurgical Treatment of Neurogenic Bladder Dysfunction

35

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35.1
Introduction

In a normal subject the urinary bladder displays an activity coordinated with the urethral sphincters. Bladder and urethral sphincters activity is modulated by the central (brain, brain stem and spinal cord) and peripheral (spinal sacral roots) nervous system, granting a normal voiding. The term “neurogenic bladder” refers to a pathological condition in which systemic and neurological congenital or acquired diseases undermine nervous control of bladder and urethral activity and determine a variety of voiding disorders. A thorough knowledge of the physiology of the bladder and urethra and of the pathophysiology of the specific voiding disorder is the basis for a suitable treatment of the neurogenic bladder and requires a careful clinical and instrumental work-up, which includes urodynamic and radiographic imaging studies.

The treatment of neurogenic bladder is at first conservative and is based on rehabilitating techniques and pharmacological therapy. In case these treatment modalities fail or determine unbearable side effects, two neurosurgical therapies with variable but recently increasing success rates are available; these are based on the concept of neuromodulation, which is the application of electrical stimulation to restore the normal physiological function of bladder and lower urinary tract sphincters and striate muscles. These two techniques, the anterior sacral root stimulation (ASARS), generally coupled to posterior rhizotomy, and the sacral nerve neuromodulation (SNM), are still applied almost exclusively to adult patients but represent promising new therapeutic tools even for paediatric patients for their mini-invasiveness, efficacy and, especially for SNM, reversibility of effects and conservativeness.

35.2
Physiology and Pathophysiology

Under normal conditions bladder presents the alternation of two phases, filling and emptying, resulting from the synchronization of detrusor and sphincters muscles functioning. During the filling phase the sympathetic nervous system (SNS), located in the lower thoracic spinal cord, inhibits the detrusor muscle activity and increases the tone of the internal sphincter, while the tone of the external sphincter is increased by a reflex arch activated by the stimulation of the pudendal nerve ensuing from bladder filling. Moreover, SNS inhibits parasympathetic nervous system (PNS), whose role is triggering bladder emptying as soon as the volume of urine surpasses the bladder voiding threshold. Once reached this threshold, stretch receptors convey to the pudendal nuclei of the sacral cord the message that bladder is filled to capacity; therefore, the external urethral sphincter and pelvic floor muscles relax, SNS stimulation of the internal sphincter ceases and the sphincter relaxes and opens. At this point sacral PNS sets off the contraction of the detrusor and intravesical pressure overcomes intraurethral pressure, resulting in urinary flow.

In children 3 years old and younger a continuous cycle of bladder filling and emptying is controlled by the sacral reflex centre. Frontal lobes take over the control of the activity of the urinary system by age 3–4 years: the signal of bladder fullness originating from stretch receptors of the detrusor muscle translates into an immediate desire to urinate, which is suppressed by the brain sending inhibitory signals to the pontine micturition centre (PMC). Inhibition of PMC results in deactivation of the voiding mechanism until a socially acceptable situation is at hand; therefore, for most of the day detrusor muscle is kept relaxed while smooth and skeletal urethral sphincters and pelvic diaphragm contract voluntarily to maintain a negative pressure gradient between bladder and urethra, which is the basis of the continence mechanism. The activity of these muscles is modulated by the PMC according to the messages sent by the brain, so that the healthy individual has the capacity to stop and start urination willingly.

Neurological diseases may affect both filling and voiding phase, depending on the location of the injury. Dysfunction of the filling phase is produced by detrusor overactivity or sphincter underactivity and results in urinary urgency or incontinence.

Dysfunction of the emptying phase is due to detrusor underactivity or sphincter overactivity and determines various degrees of urinary retention.

There are two types of urinary incontinence in neurogenic bladder: active and passive. Active incontinence is due to detrusor overactivity or hyperreflexia. It determines a rise of intravesical pressure during the filling phase with reduction of the bladder compliance and symptoms of urinary frequency, urgency or urge incontinence. This condition is determined by a suprapontine lesion that disconnects PMC from voluntary control, like intracranial acute or chronic hypertension and lesions of cerebrovascular, traumatic or neoplastic nature of the frontal lobe. In case of suprapontine lesions, skeletal muscles of external sphincter and pelvic diaphragm function normally and in synergy with the detrusor muscle. Passive incontinence, which is due to sphincter underactivity, results in a fall of intraurethral resistance. It has more frequently the characters of an overflow or stress incontinence and is generally associated to a detrusor hypo- or areflexia following sacral cord or nerve root involvement. Typical causes are herniated discs, tumours, traumas or congenital malformations causing cauda equina or conus medullaris lesion with dysfunction of the pudendal nuclei and nerves and sacral PNS.

Urinary retention, on the contrary, may depend on a condition of detrusor underactivity or urethral sphincter overactivity. Detrusor hypo-areflexia, generally associated with sphincterial underactivity, results in partial or complete inability of the bladder to empty, with urinary retention associated in a number of cases with stress or overflow incontinence and it is due to a lesion of the lower motor neuron or of sacral sympathetic nervous structures.

During the first 6–12 weeks from a suprasacral spinal cord injury, a phase known as "spinal shock", there is a transitory condition of detrusor, and rectum, areflexia, and the affected patient experiences urinary retention. It is worth noting that in this phase urethral sphincters are normal. After that time, detrusor and external and internal urethral sphincters activity escapes from the supraaxial control exerted by the brain through the PMC and reaches an overactive, spastic state, configuring the clinical picture of detrusor–sphincter dyssynergia with detrusor hyperreflexia (DSD-DH): both detrusor and sphincters contract at the same time and the affected individual experiences urge incontinence, also described as "reflex" or "spastic" incontinence. The patient senses an irresistible need to urinate and involuntarily a small amount of urine spills out frequently but, paradoxically, he/she is in urinary retention for the inability to empty his/her bladder.

Bladder and sphincteric dysfunction is generally associated with autonomic dysreflexia when the lesion is at or above the sixth thoracic vertebra. Autonomic dysreflexia is due to the lack of PNS inhibition over SNS and is then characterized by an exaggerated sympathetic response to any stimuli below the level of the spinal cord injury. Symptoms include sweating, headache, arterial hypertension and reflex bradycardia.

The most frequent neurological disease determining abnormal lower urinary tract function in young children is spina bifida. Dysraphism can produce a wide variety of neurological deficits, depending on the gravity of the defect and the extent of neural elements involvement. A common diagnosis made by urodynamic studies in these patients is detrusor hypo- or areflexia, due to the dysfunction of sacral spinal cord and peripheral nerves; however, detrusor–sphincter dyssynergia with detrusor hyperreflexia is also a possible finding. This condition, if not treated, can lead to vesicoureteral reflux in up to 40% of cases and is associated with a high risk of upper genitourinary tract deterioration, in as many as 70% of cases. The treatment of neurogenic bladder is always conservative at first, but drugs carry significant side effects and in some cases do not obviate upper genitourinary tract damage, whereas destructive and reconstructive surgical procedures suffer from significant complications. Neuromodulation has been recently proposed as a new treatment modality for neurogenic bladder dysfunction, also in paediatric patients, for its reliability, mini-invasiveness and simplicity of execution. The most acknowledged techniques of neuromodulation applied to neurogenic bladder dysfunction are the anterior sacral root stimulation (ASARS), generally coupled to posterior rhizotomy, and the sacral nerve neuromodulation (SNM).

35.3
Surgical Techniques of Neuromodulation

35.3.1
Anterior Sacral Roots Stimulation and Posterior Sacral Roots Rhizotomy

Patients with complete suprasacral spinal cord lesions show signs of DSD-DH, responsible for urinary retention and reflex incontinence: the detrusor muscle is overactive but develops ineffective contractions not coordinated to the activity of a spastic external sphincter; thus, bladder emptying is impaired with high residual volumes and its compliance is reduced, leading to a rise in the intravesical pressure and urine leakage. This predisposes to urinary tract infections with risk of upper urinary tract damage and renal failure. Affected patients in whom the caudal section of the cord and its roots are intact may be treated with implantation of a nerve root stimulator. This technique was pioneered by Brindley in the 1970s and implies the electrical stimulation of the sacral anterior roots to trigger a valid detrusor contraction, induced by the activation of small non-myelinated efferent parasympathetic nerve fibres, for emptying the bladder. Although anterior sacral root stimulation triggers also a simultaneous stimulation of the external sphincter muscle, striate muscle contracts and relaxes more rapidly than the smooth detrusor muscle; thus, the stimulator, generating intermittent stimulation bursts, can be set to deliver the peaks of contraction of the sphincter and the bladder out of phase. As a result, at the end of each burst the sphincter relaxes more rapidly than the detrusor, so that the pressure gradient between bladder and urethra is still adequate to produce micturition between the bursts. In cases of suprasacral spinal cord injury with DSD-DH, it is advantageous to use electrical stimulation of S2–S4 anterior nerve roots in combination with the posterior rhizotomy at the same levels. In fact, complete sacral deafferentation prevents reflex contractions of the detrusor muscle and restores bladder compliance, allowing large amounts of urine to be stored at a low bladder pressure, with resolution of reflex incontinence. Moreover, posterior sacral nerve roots excision interrupts the reflex arch leading to external sphincter dyssynergia and prevents autonomic dysreflexia triggered by distension or contraction of bladder or bowel; however, sacral deafferentation has its drawbacks, as it eliminates the reflexes of erection, ejaculation and defecation, although these reflexes are already compromised following spinal cord injuries and may be restored with the means of other techniques. In addition, about 15% of patients who have undergone posterior rhizotomy report stress incontinence, probably due to a decreased sphincter tone after sacral deafferentation. Furthermore, bladder emptying occurs at intravesical pressures higher than normal, with risk of vesicoureteral reflux.

The operation is performed under general anaesthesia by mean of an L4, L5 and partial sacral laminectomy. Following dura and arachnoid opening, the anterior and posterior sacral roots are identified anatomically, the posterior roots being thicker, and electrophysiologically. During electrical stimulation bladder response is monitored together with anal sphincter, pelvic diaphragm, toe flexors, triceps surae, biceps femoris and gluteal muscles response. The S2–S4 sensory roots are then sectioned. After sacral deafferentation, the electrodes can be put in contact with the extradural part of the mixed spinal nerves instead of the intradural motor roots, which decreases the incidence of cerebrospinal fluid fistula and rupture of the cables at the exit from the dura and minimizes neuroapraxia following surgical dissection of nerve roots. The electrodes' wires are then tunnelled subcutaneously and connected with a pulse generator implanted in a subcutaneous pocket made at the level of the anterior abdominal wall. Afterwards, careful adjustments are made to the stimulation parameters to optimize bladder voiding and control the rise of intravesical pressure during the emptying phase. The aim is to reach a residual volume of less than 50 ml, which results in a significant reduction of urinary tract infections, and in a decreased risk and often regression of ureteric reflux and hydronephrosis.

35.3.2
Sacral Nerve Neuromodulation

As stated previously, many patients with neurological bladder display not only a bladder paralysis, but more frequently have a situation of DSD-DH, which hinders a correct voiding and determines the presence of residual volumes of urine and sustained high intravesical pressures and reflex incontinence. Sacral nerve neuromodulation (SNM) is a recently developed therapeutic tool for neurogenic bladder dysfunction whose major advantage is both to restore bladder compliance and to promote bladder voiding while preventing high intravesical pressure, with no nerve root interruption. The goal of this technique is to achieve detrusor and urethral overactivity inhibition by chronic electrical stimulation of afferent somatic sacral nerve fibres by means of an implanted electrode connected to a subcutaneously-placed pulse generator.

The ratio of this treatment modality is based on the existence of spinal inhibitory systems which are capable of interrupting detrusor or sphincteric contraction and to restore detrusor–sphincter synergy. The stimulation of the afferent branches of the pelvic nerves and the dorsal clitoral or penile afferents of the pudendal nerves has been shown to inhibit the bladder or urethral overactivity. To explain in detail the theory of action of SNM on both urinary retention and incontinence it is important to go over the neurophysiology of the bladder and urethra. Bladder afferent nerves are critical for sending signals of bladder fullness and discomfort to the brain and initiating the micturition reflex. The bladder afferent pathways are composed of two types of axons: small myelinated A delta fibres and non-myelinated C-fibres. The former transmit signals mainly from mechanoreceptors that detect bladder fullness or wall tension, whereas C fibres mainly detect noxious signals and initiate painful sensation. Bladder hyperactivity and urinary incontinence are believed to be mediated by the loss of voluntary control of voiding and the appearance of primitive voiding reflex circuitry. It has been demonstrated that, upon interruption of the spinobulbospinal pathways of the micturition reflex, a new sacral reflex arc may become functional as a result of neuroplasticity, with an afferent limb consisting of non-myelinated C-fibres. Under normal conditions the latter are thought to be mechano-insensitive and unresponsive to bladder distension (hence, the term “silent” C-fibres); however, as a consequence of spinal cord injury, the silent C-fibres becomes sensitive to bladder distension and can trigger micturition reflexes. The new reflex circuit is responsible for detrusor hyperreflexia, probably with an increase of substance P, neurokinin A and calcitonin-gene-related peptides. As a matter of fact, sacral root neuromodulation seems to be effective on urinary incontinence by inhibiting the activity of the reflex arc conveyed by the C-afferent fibres. The reduction in the neuropeptide content may explain the long-time neuromodulation effect of SNM.

The SNM is also effective on urinary retention through a double mechanism: first it eliminates the detrusor overactivity, as already said, increasing the bladder compliance, which translates into resolution of reflex incontinence. The second effect of SNM is based on the existence of an important bladder–urethra reflex that is mediated by sympathetic efferent pathways to the urethra and triggered by the bladder filling. This excitatory reflex contracts the urethral smooth muscle (internal urinary sphincter) and is thus termed a “guardian reflex”. A second guarding reflex is triggered by the bladder afferents that synapse with sacral interneurons which, in turn, activate urethral external sphincter efferent neurons that send axon into the pudendal nerve. The activation of pudendal–urethral efferent pathways contracts the external urinary sphincter. The spinal guarding reflexes can be turned off by the brain for urination to take place. In case of neurological disease, the brain cannot turn off the guardian reflex and retention can occur. Before the development of brain control micturition, stimulation of somatic afferent pathways passing through the pudendal nerve to the perineum can initiate efficient voiding by activating bladder afferent pathways and turning off the bladder–sympathetic reflex component of the guardian reflex mechanism. It is hypothesized that SNN can elicit similar responses in patients with urinary retention and can restore micturition by inhibiting the guardian reflexes.

The implantation of a sacral nerve neuromodulation device consists of two steps:

1. Peripheral nerve evaluation (PNE)
2. Permanent implantation of electrode and pulse generator

35.3.2.1
Peripheral Nerve Evaluation

Peripheral nerve evaluation implies a temporary application of neuromodulation and it is both a diagnostic and a therapeutic tool: it provides accurate information about location, integrity and function of the sacral nerves and about improvement of symptoms and quality of life after the eventual implant of the stimulator. The PNE is carried out in two phases: acute neuromodulation and subchronic neuromodulation.

35.3.2.2
Acute Neuromodulation

With the patient placed in prone position and under local anaesthesia a foramen needle is inserted into one or both dorsal foramina of the S3 segment for acute stimulation of the sacral nerve with graduated amplitude. Stimulation is initially done with a low frequency (10–25 Hz) and a duration of the train pulses of 210 µm. Typical responses at S3 are “bellows” movement of perineum, plantar flexion of the great toe and sensation of pulling in the rectum, vagina, labia or scrotum. Since several patients with upper motor-neuron lesions have sensory troubles, often only motor responses are evocated by stimulation. Foramen needle stylet is then removed and a temporary unipolar electrode for subchronic modulation is threaded into the sacral lumen until resistance from tissue beyond the needle tip is met. After a new stimulation for verifying the correct position of the temporary electrode, the needle is withdrawn and the electrode is secured to the skin using a membrane dressing.

35.3.2.3
Subchronic Neuromodulation

The purpose of subchronic neuromodulation is to assess the therapeutic value of neurostimulation. It is currently performed over a period of 7–10 days with temporary implanted electrode connected to an external neurostimulation device. During this period the patient writes up a comprehensive diary concerning voiding function (leakage episodes, pad use, spontaneous void volume, intermittent self-catheterization voided volume).

The efficacy of subchronic sacral neuromodulation is assessed by changes in the symptoms and urodynamic findings. In patients with bladder incontinence the procedure is considered successful if the clinical symptoms and signs are alleviated by at least 50%, and in patients with retention if it allows a micturition with less than 50 ml of residual urine volume.

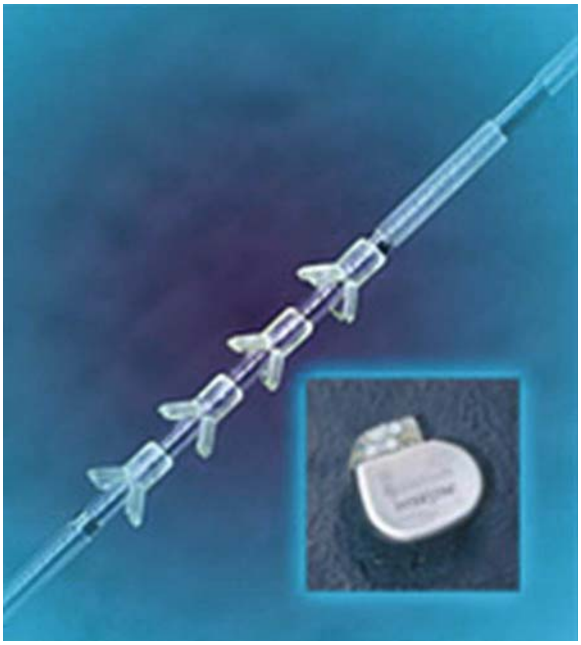

Fig. 1. Definitive quadripolar sacral electrode for sacral nerve neuromodulation

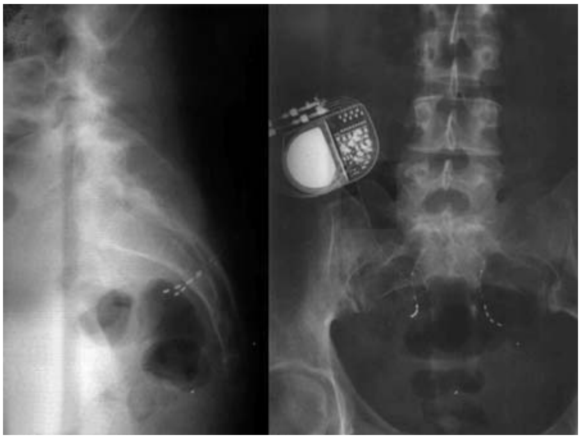

Fig. 2. Control X-ray shows the position of the pulse generator and of the electrodes in S3 roots foramina.

35.3.2.4
Permanent Implantation of Electrode and Pulse Generator

The foramen needle is inserted into the S3 foramen following the same procedure and an electrical stimulation and fluoroscopy controls are obtained to verify its correct position. A guide is then inserted through the needle and the needle is removed. The guide wire serves as a guide for a metal dilator and then for a plastic dilator through which a quadripolar stimulation lead is inserted to the desired location (Fig. 1). The correct positioning is verified with stimulation and fluoroscopy (Fig. 2), the plastic dilator is removed and the lead is fixed in place by creating an incision through the skin, anchoring the lead to the fascia layer. For the pulse generator a 5- to 6-cm-long transverse incision is made over the posterior superior quadrant of the gluteal region. Below the subcutaneous fat, a pocket is created: the pulse generator is placed in this pocket and connected to the sacral lead. Parameters programmed on pulse generator for chronic stimulation are: frequency 25 Hz, pulse duration 210 µm and amplitude 1–10 mA. The stimulation mode is cyclic with 5 s on and 5 s off, active night and day; the stimulation polarity is monopolar or bipolar.

Advantages and disadvantages of each neuromodulation procedure should be carefully weighted in consideration of the individual clinical condition and pathology before proposing it as a treatment. Even if neuromodulation has acknowledged advantages due to its very specific and limited effects, which can also be reversible and easy to adapt to the individual condition of the patient, it has nonetheless some drawbacks, as it requires a surgery and can be subject to breakage and deterioration of the material. A study by Hoebecke et al. [16] shows how transcutaneous neuromodulation can improve urge incontinence in children with detrusor overactivity, and more recently, Guys et al. [15] report a trend toward a clinical and urodynamic improvement in paediatric patients with neurogenic bladder due to spina bifida undergone to permanent SNM. Although more studies about the application of neuromodulation in paediatric patients are needed, it is conceivable to propose this treatment for cases refractory to a more conservative treatment before any major surgery is undertaken.

35.4
Conclusion

Neuromodulation is an appealing new technique that can be proposed even to treat paediatric neurogenic bladder dysfunction in view of its usefulness and mini-invasiveness. Further technological improvements, including the production of miniaturized, more flexible and resistant electrodes, more stable and empowered integrated circuits and the application of telemetry for computerized setting of the stimulators and transfer of data, will likely broaden the indications of neuromodulation, which could become the standard treatment option for neurogenic bladder dysfunction.

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Management of Orthopedic Problems in Pediatric Patients with Neurogenic Bladder Dysfunction

36

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36.1
Introduction

Paediatric urological, orthopaedic and neurological surgeons have a common culture of “peripheral neurological pathologies” (PNP) in children. Collaboration between these different specialists is immediately relevant for patients for whom the malformative diagnosis is obvious, such as a myelomeningocele or an important lumbo-sacral agenesis; otherwise, this is discovered by one of the three specialists, depending on their area of expertise, and leads to a possible PNP diagnosis, for which further examinations are performed in collaboration with their colleagues. A very complete urological, neurological, and orthopaedic assessment is essential before any treatment.

36.2
Clinical Signs Suggestive of a PNP

36.2.1
Neurological Examination

In conducting a clinical evaluation we have to search for weakness, paresthesia, abnormal abdominal reflexes, clonus, hyperreflexia, asymmetric deep tendon reflexes and diminished rectal tone.

36.2.2
Cutaneous Examination

The skin has to be examined on the medial line from the buttocks to the hair roots. Then, the scalp has to be examined on the medial line, and this investigation has to be continued to the root of the nose. The examiner will be looking for a flat or a tuberous angioma, a hypertrichosis from a high density of hairs to real tufts, a small cutaneous tumour, or a naevus. All these abnormalities can be associated with each other. A dermal sinus must also be considered, which has to be differentiated from a blind dimple which is always located in front of the top of the coccyx, and from a pilonidal cyst which is an adult pathology.

36.3
Orthopaedic Examination

36.3.1
The Spine

Any discovery of a spinal deformity has to be carefully analysed with a peripheral sensory, motor, and sphincteral neurological exam in order to find an associated abnormality. An antero-posterior and profile radiographic assessment of the whole spine, in standing position if the child can walk, will reveal any osseous spinal abnormalities which will allow to diagnose a congenital scoliosis.

These abnormalities are usually classified in formation defect with hemivertebra (HV) as a basic deformity, in segmentation defect with intervertebral block as a basic deformity, and in complex defect with vertebral jigsaw as a representative abnormality [8].

The discovery of such spinal abnormalities (all the more if the peripheral neurological exam is abnormal) will prove the completion of complementary investigations such as a vertebro-medullary magnetic resonance imaging (MRI).

From 1980 to 2003, a consecutive series of 75 patients with 80 HV responsible for evolutive congenital scoliosis or kyphoscoliosis were personally managed by HV resection using a double approach and a short anterior and posterior convex fusion [7]. All but 10 patients had preoperative MRI of the spine to exclude intrathecal abnormalities and to study the segmentation of the HV and the growth plate; the 10 others had myelography (in the beginning of the series). All children underwent renal ultrasound preoperatively to assess associated congenital renal system abnormalities. A careful cardiac evaluation was performed with echocardiography in case of abnormality.

Associated genitourinary abnormalities were found in 24% of patients, cardiac abnormalities in 8% and intrathecal abnormalities in 15%. The intrathecal abnormalities consisted of six tethered spinal cords, three syringomyelias, one amputation of distal conus, two meningoceles and one myelocystocela. One patient had association of tethered spinal cord and syringomyelia, and another patient had association of meningocele and tethered spinal cord. Medullar abnormalities were more frequent in case of vertebral malformations at the lumbosacral level compared with the thoracic or lumbar levels. There was no statistical difference concerning frequency of medullar-, cardiac- or genitourinary-associated abnormalities between single or multiple vertebral malformations, nor between segmented or semisegmented HV, nor between right- and left-sided HV, nor between males and females.

In our study, intrathecal abnormalities were found in 15% of the patients. McMaster reported intraspinal abnormality in 18% of 251 patients with myelography [19]. Using MRI, Bradford et al. found intraspinal abnormality in 38% of 42 patients [9], Suh et al. in 31% of 41 patients [29], Prahinski et al. in 30% of 30 patients [24], Basu et al. in 37% of 126 patients [4]. Basu et al. showed also that the HV located higher up in the spine (cervical or thoracic) had higher risk of intraspinal abnormalities [4]. In our series, medullar abnormalities were more frequent at the lumbo-sacral level compared with thoracic or lumbar levels [7].

Using ultrasound, we found genitourinary abnormalities in 24% of children. This rate is similar to the one reported in the literature. Using intravenous urography (IVU), MacEwen et al. found genitourinary abnormality in 20% of patients with congenital scoliosis [18]. Using IVU and ultrasound, Guerrero et al. [13] found an incidence of genitorinary abnormalities of 34% Using renal ultrasound, Basu found an incidence of urogenital abnormality in 21% [4]. In our series genitourinary malformations are more frequent at higher levels, but this is not significant. Beals et al. also found that location of the vertebral malformation did not correlate significantly with associated abnormalities in the genitourinary system [5].

In the absence of spinal abnormalities, and before diagnosing any idiopathic scoliosis, it is worth citing the work of Davids et al. [11]. In their research, among 1280 children with presumed adolescent idiopathic scoliosis, MRI was ordered for 274 children (21%). Indication for MRI was abnormal neurological finding and/or abnormal curve pattern such as left thoracic, short-segment scoliosis, decreased vertebral rotation, absent apical segment lordosis or rapid curve progression. Abnormal findings were seen in 27 (10%) of the 274 patients who underwent imaging, or 2% of the entire cohort. The most valuable single indicator of an abnormal finding on MRI was absence of thoracic apical segment lordosis: 8 of 39 patients with that indicator had an abnormal finding on MRI. The optimal diagnostic yield for a single category of indicators occurred when an atypical curve pattern was the only indicator: 6 of 58 patients in whom this was the case had an abnormal finding on MRI. The optimal diagnostic yield occurred when both an atypical curve pattern and neurological indicators were present: 13 of 53 patients in whom this was the case had an abnormal finding on MRI.

36.3.2
The Pelvis

Apart from an evident pelvic malformation, the paediatric orthopaedic surgeon will look for an asymmetry of motion and/or a hip instability, because a neurological pathology can lead to an asymmetry of muscular activity of muscles stabilizing the hip with an instability as a consequence. This instability can be seen after the neonatal period.

An erroneous diagnosis of congenital hip luxation will be corrected subsequently because of the difficulties in obtaining a reduction and/or a stabilization of this hip, and/or because of the outbreak of other peripheral neurological signs. The diagnosis of paralytic hip luxation will then be done.

36.3.3
The Lower Limbs

Apart from neurological signs which were previously described, one will look for an amyotrophy of the thigh or the leg. This amyotrophy, when it is associated with a leg-length discrepancy, can be the discovery method of an underlying neurological pathology.

It has to be differentiated from corporal hemi-hypertrophies, which are frequent in children and which are not accompanied by underlying neurological pathology.

Any motion asymmetry of the hips or knees, in particular an abduction deficit of the hip or a knee flexion contracture, must lead the examiner to look for an underlying neurological pathology.

36.3.4
The Feet

Sometimes foot deformation is obvious, such as in equinovarus. As with the hip, an erroneous diagnosis of congenital clubfoot can be made, when in fact it may be a neurological equinovarus foot due to an asymmetry of muscular activity.

A direct foot equines can be the discovery method of an underlying neurological pathology. This equines can be slight, at least in the beginning of growth, and may reflect a simple deficit of foot dorsiflexion in comparison with the other side.

Any unilateral or bilateral deep foot in a child has to be considered as the consequence of an underlying neurological pathology. The diagnosis of an idiopathic deep foot should be made only after a meticulous aetiological assessment while looking for a neurological pathology.

36.4
Synthesis

In addition to diagnoses of obvious malformations from birth, the paediatric orthopaedic surgeon should request complementary examinations in his/her search for a neurological pathology (see Fig. 1).

36.5
Management of Orthopaedic Problems

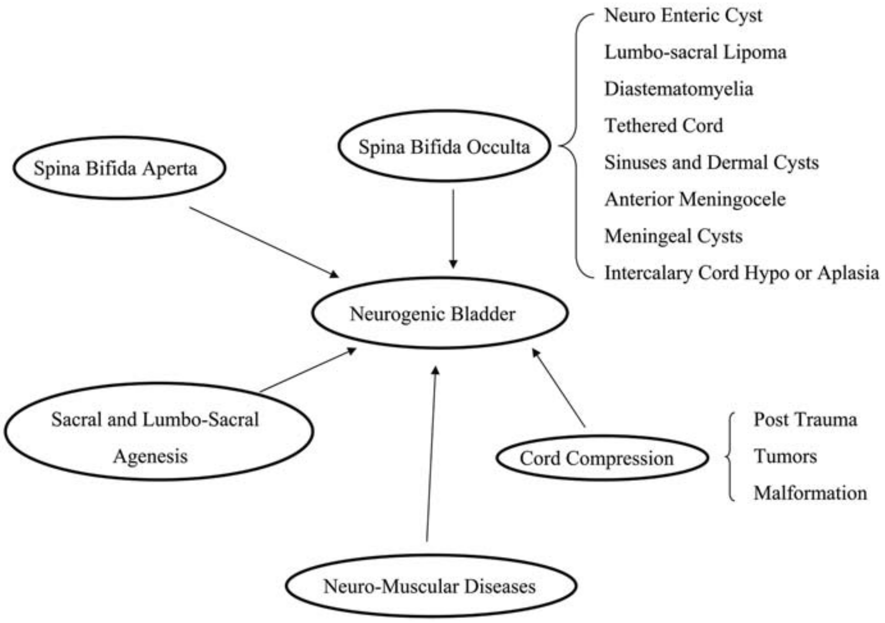
36.5.1
Spine

36.5.1.1
Scoliosis

Because a high percentage of curves in congenital scoliosis are progressive and non-responsive to bracing, operative treatment is the mainstay of care. The three basic operations are fusion in situ, convex growth arrest (epiphyseodesis) and HV resection [24].

Isolated posterior fusion with or without instrumentation is not recommended for young children, because correction is limited and a crankshaft phenomenon of the spine occurs in 15% of patients and in 36% when age at surgery is <4 years, as revealed in a series of 31 pa-

Fig. 1. Main causes of neurogenic bladder



tients treated with posterior fusion (using Harrington instrumentation in 18 and without instrumentation in 13 patients) [16]. Hall et al. reported a reduction of the average curve from 62 to 40° and from 43 to 38°, respectively [15]. Combined anterior and posterior fusion adds the potential benefit of greater correction, and of correction in the sagittal plane, because the excision of discs allows for greater mobility of segments. It also decreases the likelihood of pseudarthrosis and prevents crankshaft phenomenon by removing the growth plates.

Cheung et al. reported a long-term follow-up (10.8 years) of a series of six thoracolumbar HV cases treated by convex fusion combined with instrumented concave subcutaneous distraction [10]. They reported a mean improvement of 41% from 49 to 29° at the latest follow-up assessment.

Convex growth arrest or epiphyseodesis on the convex side is appropriate only for patients with growth potential remaining on the concave side. This procedure must be done early (before 5 years of age) and before the curve has progressed beyond 50 or 60° [30, 32]. Taking into account the 123 patients reported in the literature treated with this technique [31, 32], the technique gives an improvement (epiphysiodesis effect) in 48% of cases (20–77%), no change (fusion effect) in 40% (17–70%) and progression in 12% (0–21%) of cases. To obtain epiphysiodesis effect, two levels above and below the HV have to be fused. In lumbar spine it should represent an important loss of mobility of the lumbar segment. Marks et al. concluded that combined anterior and posterior convex spinal growth arrest alone does not prevent progression of deformity in infantile idiopathic scoliosis, and that the addition of posterior instrumentation can retard or arrest deformity progression but not reverse it [20].

The HV excision was first done in 1921 by Royle in Australia [26]. Numerous authors have reported series of HV resection using successive or simultaneous anterior and posterior approaches, or posterior approach alone [17, 27]. Improvement rates vary in these studies from 24.3 to 71.1% (Fig. 2).

Apart from these three basic interventions for evolutive congenital scoliosis, a new technique, rib's distraction, has been proposed. This technique is especially useful in cases of complex congenital thoracic spine malformations associated with rib's hypoplasia or aplasia.

36.5.1.2
Kyphosis

Congenital kyphosis is often associated with intraspinal neurological malformations. For evolutive congenital kyphosis early surgery is indicated. Posterior arthrodesis is indicated when performed before 3 years of age in mild angular kyphosis. For major kyphosis two options are available: first is to perform anterior disc excision plus anterior distraction and anterior plus posterior arthrodesis. The second option is to perform a posterior closing wedge osteotomy followed by posterior compression instrumentation plus arthrodesis.

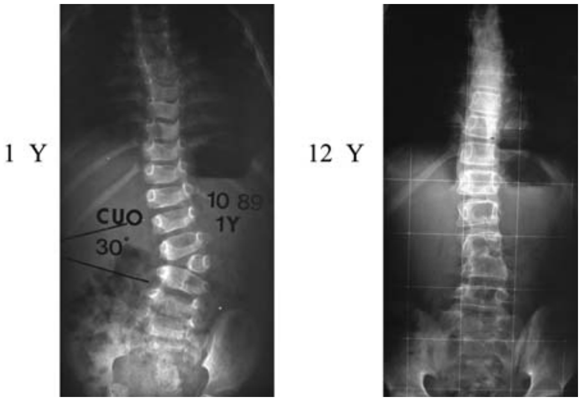


Fig. 2. Hemivertebra exeresis. **a** One year of age, prior to surgery. **b** Eleven years, follow-up

Apart from the congenital kyphosis, the neurosurgeon must be aware of the risk for an iatrogenic kyphosis after either laminectomy or laminotomy. Laminotomy is often indicated in these patients to treat the associated intraspinal abnormality.

After laminotomy in children, when the laminotomy extend from occiput to at least C3 or in the thoracic or thoraco-lumbar area, the patient has to wear a brace for at least 6 months. Then a 6 months frequency follow-up is mandatory to detect any evolutive kyphosis.

In case of iatrogenic evolutive Kyphosis, despite bracing, there is an indication for posterior arthrodesis.

36.5.2
Hip

Splinting in paralytic dislocated hip is usually unsuccessful. As far as muscular activity around the hip remains unbalanced, hip stability is compromised. It is often necessary to perform open reduction and femoral plus pelvic osteotomies, and at the same time to balance muscle activity by tenotomy and/or muscle transfer. Indication for hip surgery depends on the ambulatory status of the patient.

36.5.3
Limb Length Inequality

For minor limb length inequality (i.e. <2 cm at the end of growth) there is no indication for treatment, except a shoe lift. If the inequality is calculated to reach between 2 and 4 cm at the end of growth, the easier way to get balanced is to perform an epiphyseodesis of either the distal femoral physis or the proximal tibial one. Depending on the amount of centimeters of inequality and the age of the patient, it is sometimes necessary to perform both distal femoral and proximal tibia epiphyseodesis. Anderson graphs and dedicated software are used to decide at what age epiphyseodesis must be done.

36.5.4
Foot

Paralytic club foot is more difficult to correct by manipulation and/or cast than congenital club foot. Daily manipulation of the feet or serial-cast treatment are mandatory at birth. There is a high risk of recurrency during growth, since extrinsic muscle activity is not rebalanced. If surgery is indicated, due to a residual or a recurrent deformity, the surgeon has to add to the classic surgical correction of a congenital club foot tendon transfer to restore balanced muscle activity.

Another pattern of the foot's deformity is medial pes cavus. Due to the first contact between the foot and the floor, on the head of the first metatarsal bone the forefoot as well as the hindfoot turn in a varus position. Varus of the hindfoot is reducible at the pre-adolescent age, but it becomes progressively irreducible unless the forefoot was previously corrected by extension osteotomy of the first ray of the foot plus plantar aponevrosis release.

At the end of the growth spurt, if the deformity remains, a triple arthrodesis might be indicated.

36.6
Management of Specific Orthopaedic Problems

36.6.1
Sacral Agenesis

Sacral agenesis is a rare condition that consists of partial or complete absence of the sacrum. With minimum orthopaedic interventions, almost all of the patients become community walkers, usually without aid. Lumbosacral agenesis is a somewhat rarer condition that consists of the absence of part, or all, of the lumbar spine and sacrum, with ilio-lumbar dissociation and instability. In these patients "arthrogrypotic-like" deformity of the lower limb, including paralytic hip dislocation, flessum knee contracture, foot deformity and paraplegia, are present.

Based on previous classifications and our own experience with 56 thoraco-lumbo-sacral, lumbo-sacral and sacral ageneses, we propose the following classification (Fig. 3) [6]:

1. Group 1: total sacral and variable lumbar or thoraco-lumbar agenesis. The caudal end plate of the lowest vertebra resting above either fused ilia or an iliae amphiarthrosis. The ilia can also articulate with the sides of the lowest lumbar present in the vertebra.
2. Group 2: sacro-iliac dysgenesis. One of the two sacro-iliac joints is agenetic or dysgenetic leading to an instability of the sacro-iliac joint. We have assessed this deformity through 18 computed tomography scans performed in sacral agenesis. On the side of the unstable sacro-iliac joint, if the gluteus muscles work, the iliac wing rotates inward pulled by the glu-

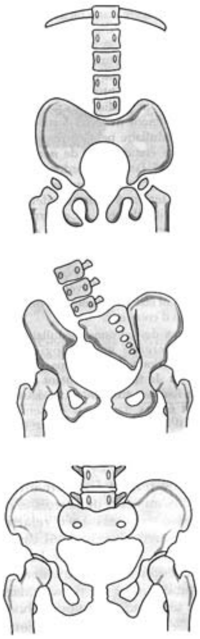


Fig. 3. Orthopaedic management according to our personal classification in sacral agenesis

Type I : Spino-iliac is seldom indicated.
For patients with motor paraplegia do not perform
with flexed knees

Type II : Ambulatory Patients. Surgery is indicated if orthopaedic
lower limb deformities are present

Type III : Very few, if any, orthopaedic deformities teus medius. At the same time, the two first sacral vertebrae move down and back inducing a congenital scoliosis.

3. Group 3: sacral agenesis with two stable sacro-iliac joints and partial or complete agenesis below S2. We have excluded from our classification the dysraphic group with posterior meningocele or myelomeningocele.

Guille et al. proposed a new classification of lumbo-sacral agenesis [14]. Group I (corresponding to our group 1) had lumbo-sacral agenesis alone. He divided this group I into three sub types;

1. Type A: There was either a slight gap between the ilia or the ilia were fused in the midline. One or more lumbar vertebrae were absent. The caudal aspect of the spine articulated with the pelvis in the midline, maintaining the vertical alignment of the spine.
2. Type B: The ilia were fused together, some of the lumbar vertebrae were absent, and the most caudal lumbar vertebra articulated with one of the ilia, with the most caudal aspect of the spine shifted away from the midline.
3. Type C: There was a total agenesis of the lumbar spine, the ilia were fused together, and there was a visible gap between the most caudal intact thoracic vertebra and the pelvis.

Group II had a lumbo-sacral agenesis and a concomitant myelomeningocele. In their conclusion, Guille et al. emphasized that all group-I type-A patients should have correction of lower-extremity deformities as they have a very good potential to walk [14]. The other patients should have operations on the lower extremities only if the deformities preclude sitting or wearing shoes or a brace.

According to our classification, in group I, only the patients with motor-level function of the quadriceps strong enough to allow verticalization are chosen to have correction of lower-extremities deformity.

For patients with severe deformities of lower limb (absent quadriceps function, patient sits in a cross-legged position, the femora abducted in a coronal plane and the knees flexed at 60°) Aitken [1], Frantz and Aitken [12], and Russel and Aitken [28] recommended bilateral subtrochanteric amputation and early prosthetic fitting. Philips et al. stated that knee disarticulation, rather than subtrochanteric amputation and prosthetic fitting, is the most effective treatment [22]. Banta and Nichols state that preserved sensation and proprioception [3], present in most of the cases, warrant preservation of the limbs.

Andrish et al. [2] agrees with Banta et al. [3] that subtrochanteric amputations have been overemphasized as part of the routine management of these patients, and we support this statement.

Perry et al. [21], and Pirkey and Purcell [23], recommend spinal–pelvic fusion because it allows patients to sit with the hands free, permits stretching of the hip-flexion contracture, and protects the viscera from non-physiological compression. For Philips et al. [22] and Andrish et al. [2] spinal–pelvic fusion cannot be recommended because it may cause problems with hip-flexion contracture that previously were compensated for by the hypermobile spinal–pelvic junction. Seventeen of Philips et al.'s 19 surviving patients sit without support and have no apparent problems [22]. We agree with Philips et al. and do not recommend pelvic–spinal fusion.

For hip dislocation, Renshaw thinks that many surgical procedures in some patients are justified to avoid the pain [25], breakdown of the skin and increased pelvic obliquity. The benefits of reduction of dislocated hips in patients with lumbo-sacral deformity may not be worth the risk of having painful stiff hips resulting from aseptic necrosis of the femoral head or infection. In our opinion, indication for reduction of a dislocated hip is ambulatory-status patient or painful hip.

For scoliosis, bracing is difficult when spinal–pelvic instability is present. Congenital scoliosis is treated according to the general considerations described previously, as are foot deformities in ambulatory patients, or for cosmetic reasons.

36.6.2
Spina Bifida Occulta

36.6.2.1
Neuroenteric Cyst

Of 63 cases listed in the literature, two-thirds were cervico-thoracic, and over half were discovered in adults. Five cases were revealed through meningitis.

Cervico-brachial neuralgia, stiff neck, as well as mono-, para- or tetraplegia, have also been described. The clinical signs are often cyclic. Exeresis of these cysts is often difficult, due to close adhesion to the spinal cord which explains some recurrencies.

36.6.2.2
Dermal Sinuses

Dermal sinuses can involve the whole cerebro-medullary axis from the nose with the nasal dermal cyst through the occipital dermal cyst; however, they are predominantly located in the lumbo-sacral area. They are practically always, although not exclusively, on the midline. Complication, such as meningitis, often leads to the diagnosis.

36.6.2.3
Anterior Meningocele

The anterior meningocele may occur anywhere in front of the spinal column, including the cervical segment, although they are mostly sacral, with a characteristic aspect of "fish-hook"-type sacrum. Exeresis can be performed either by posterior approach, through laminotomy, with simple ligation of the neck of the cyst after suction of the pelvic content, or by a combined anterior and posterior approach.

36.6.2.4
Lumbo-Sacral Lipomas and Tethered Cord

Lumbo-sacral lipomas are almost always associated with a tethered cord, even if a tethered cord can exist without any associated lipoma. Whether surgery must be performed to prevent any further aggravation, or whether it is better to wait for the aggravation to subside, is still being debated.

36.6.2.5
Diastematomyelia

Diastematomyelia is often associated with hypertrichosis and congenital scoliosis. Exeresis of the septum and release of an associated tethered cord is not always indicated, even if a spinal arthrodesis is to be done. In our opinion, exeresis of the septum and release of an associated tethered cord is indicated in case of recent neurological aggravation or when a major straightening of the spine is predicted.

36.6.3
Myelomeningocele

Two groups of patients suffering from a myelomeningocele need little or no surgical orthopaedic assistance. The first one concerns the most severely handicapped children with lesions at or above the third lumbar vertebra who are totally paraplegic. These patients usually present with few orthopaedic deformities, except for spinal deformities. It is unnecessary to address hip dislocation, flexed knee or foot deformity, as these patients will be confined in the future to a wheelchair. Surgery may be indicated for paralytic scoliosis or kyphosis (for the thoracic forms). Physiotherapy, casts, and braces are the usual tools for treating these patients.

The second type of myelomeningocele with few deformities consists of patients with sacral myelomingocele. The only orthopaedic problem, if any, is represented by foot deformity. The patients who need orthopaedic assistance are mostly the ones with lesions between L3 and L5. Hip dislocation, flessum knee contracture and paralytic club foot are the common features for this group of patients. Most of these patients will be able to stand and walk in their adult life, with mild (if any) or more significant orthotic devices. The deformities need to be corrected according to the general guidelines we present herein.

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Fetal Surgery for Myelomeningocele

37

Hanmin Lee · Craig T. Albanese

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37.1
Overview

Myelomeningocele (MMC), the most severe form of spina bifida, affects approximately 1 in 2000 live births in the United States [1]. This birth defect occurs in the third week of gestation as the primitive neural tube forms. Failure of closure of the neural tube leads to a flat neural placode which is exposed to the amniotic fluid through a posterior defect. The etiology of MMC is believed to be multifactorial. Maternal folate deficiency correlates with an increased incidence of MMC. Maternal oral folate supplementation decreases the incidence of MMC by as much as 70% and is now widely used by women of child-bearing age [2, 3]. Fetal exposure to a variety of toxins, including carbamazepine, valproic acid, cytochalasins, calcium channel blockers, and hyperthermia, has been implicated in the development of MMC [4]. Genetic anomalies may have a role in the development of neural tube defects. The MMC is associated with trisomies 13 and 18 as well as Waardenburg's syndrome [5]. Interestingly, homologous mutations in the PAX3 gene are seen in human patients with Waardenburg's syndrome and MMC, and in splotch mice that develop neural tube defects [5].

The clinical manifestations of MMC are profound. While not initially life-threatening, as many as 25% will die by adulthood from respiratory, ventricular shunt, and urinary tract complications [6]. Nearly all infants with MMC have an associated Chiari malformation, and the majority of children develop hydrocephalus requiring lifelong ventricular decompression. Many children are delayed in reaching cognitive milestones. Depending on the spinal level of the defect, affected children may develop paraplegia, somatosensory loss, neurogenic sphincter dysfunction of bowel and bladder, sexual dysfunction, and musculoskeletal deformities.

The clinical sequelae of MMC are believed to result from a two-hit hypothesis [7]. The first hit is the failure of appropriate neurulation, and the second is the exposure of the neural elements to the amniotic fluid causing chemical and mechanical trauma. This hypothesis has led to treatment targeted at minimizing traumatic injury by fetal repair of MMC.

37.2
Fetal Surgery

Surgical creation of myelomeningocele in rodent, large animal, and non-human primate models caused paraplegia and incontinence, while immediate closure of the spinal defect resulted in normal animals [8–14]. Hindbrain herniation, akin to the Chiari malformation, has been shown to occur in a surgically created sheep MMC model, whereas fetal repair prevented hindbrain herniation [15]. These promising animal experiments led to human fetal interventions for MMC. The MMC is the first non-lethal perinatal birth defect for which fetal surgery has been performed. Because of maternal risk, fetal surgery had previously been reserved for diseases that had a significant perinatal mortality such as select fetuses with congenital diaphragmatic hernia, twin–twin transfusion syndrome, urinary tract obstruction, congenital cystic adenomatoid malformation, and sacrococygeal teratoma. To minimize maternal morbidity, the first repairs in humans were independently attempted with a fetoscopic technique by the groups at Vanderbilt University Medical Center (VUMC) and the University of California, San Francisco (UCSF) [16, 17].

The VUMC group reported four fetoscopic repairs which involved a maternal laparotomy, and a three-port fetoscopic technique. Amniotic fluid was withdrawn and replaced with CO_2 for visualization. The defect was covered with a maternal skin graft. Two fetuses died from preterm labor. No graft could be identified in the two infants who delivered near term. The efficacy of a maternal skin graft in this setting remains unclear.

The UCSF group reported three cases, two of which had to be converted to an open hysterotomy. There were two deaths in this series: one from a spontaneous abortion, and the other from postnatal urosepsis. An alloderm patch was used to close the defect in the one case that was completed fetoscopically. The patch incompletely covered the neural defect at birth and the infant required re-repair and a ventriculoperitoneal shunt.

After these suboptimal initial fetoscopic results, the VUMC group began open fetal MMC repairs in1997 and subsequently reported their experience, concluding that an open approach was superior. But the initial reports did not show an improvement in lower extremity motor or bladder function; however, the group at VUMC showed a decrease in the need for VP shunting in children who had undergone fetal repair as compared with historic controls. Bruner et al. reported a 59% shunt rate in 29 patients undergoing fetal repair as compared with 91% in the historical postnatal group [18]. While promising, these data were limited by the use of historic controls as a comparison group. In addition, the criteria for shunting were not standardized, and as many of the patients undergoing fetal surgery subsequently had postnatal care at other medical centers, even patients in the fetal surgery group had no uniformity of decision-making regarding the need and timing of a VP shunt; however, these data were validated, albeit retrospectively, by the group at the Children's Hospital of Philadelphia (CHOP) [19, 20].

There has been no report of maternal mortality from maternal-fetal surgery for meylomeningocele. The morbidity, however, is not insignificant, as women undergo two hysterotomies within several months, and require tocolytic therapy.

37.3
Clinical Trial

The aforementioned data have led to an ongoing multi-institutional clinical trial at VUMC, UCSF, and CHOP. This randomized prospective trial compares fetal repair of a MMC to postnatal repair. The trial's inclusion/exclusion criteria are detailed in Table 1.

Table 1. Inclusion and exclusion criteria for the ongoing myelomeningocele (MMC) clinical trial in the United States

Inclusion criteria
- Myelomeningocele at level T1 through S1 with hindbrain herniation
- Maternal age 18 years or older
- Gestational age at randomization of 19 to approximately 25 weeks

Exclusion criteria
- Non-resident of the United States
- Multifetal pregnancy
- Insulin-dependent pregestational diabetes
- Fetal anomaly not related to MMC
- Kyphosis in the fetus of 30° or greater
- Current or planned cerclage or documented history of incompetent cervix
- Short cervix (<20 mm)
- Placenta previa or placental abruption
- Body mass index 35 or greater
- Previous spontaneous delivery prior to 37 weeks of gestation
- Maternal-fetal Rh isoimmunization, Kell sensitization, or neonatal alloimmune thrombocytopenia
- Maternal HIV or hepatitis-B-status positive
- Known hepatitis-C positivity
- Uterine anomaly such as large or multiple fibroids or müllerian duct abnormality
- Other maternal medical condition which is a contraindication to surgery or general anesthesia
- Patient does not have a support person
- Inability to comply with travel and follow-up requirements

The trial's primary outcome variable is the need for a VP shunt at 1 year of age.

One of the sources of greatest morbidity and mortality in children with MMC is complications in the urinary tract. Most children with MMC are incontinent of urine due to abnormal innervation. Clinical manifestations include incontinence, or functional bladder outlet obstruction secondary to bladder/sphincter dyssynergy or a flaccid bladder. Historically, these patients developed progressive bladder dysfunction and deterioration of renal function; however, the advent of clean intermittent catheterization (CIC) in 1971 revolutionized the care of children with neurogenic bladders [21].

Subsequent studies have shown the efficacy of antibiotic prophylaxis and anticholinergic therapy in preserving urinary tract function [22]. The regimen of CIC with antibiotic prophylaxis and aggressive management of urinary tract infections has been shown to effectively preserve renal function [23]. Approximately 70% of patients with neurogenic bladders can now maintain continence with this regimen; the remainder need surgical intervention to augment the bladder or to improve sphincteric function. Stomach, small intestine, or colon can be used for bladder augmentation. Artificial sphincters, aponeurotic slings, and bladder neck tubularization can be used to improve sphincter function. Continent diversions, principally the Mitrafanoff procedure, using the appendix as a continent catheterizable conduit, allows for easier bladder access. Presently, the goal for patients with MMC with regard to the urinary tract is targeted at preserving renal function and achieving urinary continence with medical management and surgical intervention, when necessary.

Recently, the United States government funded a complimentary study to the fetal repair trial that will examine the effect of *in utero* repair on postnatal bladder function. This underscores the significance of the various urinary tract complications associated with MMC. All patients enrolled in the clinical trial will be eligible for the urology supplement. The primary outcome variable of the urology study is to determine if intrauterine repair of MMC improves urological outcome. This determination comes from a composite of three variables: (a) the need for long-term CIC up to 30 months of age; (b) recurrent urinary tract infection; and (c) death. In addition, urodynamic studies will be performed to determine if fetal repair affects bladder capacity, leak-point pressure, and the need for vesicostomy or urethral dilation. The protocol used to manage newborn infants in the trial will consist of the following: (a) urinalysis, urine culture, and sensitivity within the first 48 h of life and before antibiotic administration; (b) renal and bladder ultrasound within the first 48 h of life, before repair if possible; (c) urodynamic studies before discharge; and (d) CIC for 48 h postnatally in the fetal repair group and for 48 h postoperatively in the postnatal repair group, unless the infant is less than 1500 g or younger than 30 weeks of gestation at birth.

37.4
Conclusion

Myelomeningocele is a morbid disease with a significant mortality within the first several decades of life. Fetal surgery is a promising therapy to prevent progressive neurological dysfunction. Unfortunately, fetal repair has not been shown thus far to improve leg or bladder function. Data from VUMC and CHOP suggest that hindbrain herniation and the need for VP shunting may be decreased. These potential improvements must be balanced with maternal safety considerations. The current funded trial in the United States will provide answers about the efficacy of fetal surgery for this disease, and, just as importantly, will provide the best data about the efficacy of the current multidisciplinary methods of treatment for MMC and the outcome of these children.

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Infectious Complications of Neurogenic Bladder in Children

38

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38.1
Introduction

Children with neurogenic bladder are susceptible to many factors which collaborate together for the deterioration of the upper urinary tract resulting in renal insufficiency and chronic renal failure. Among these factors are the inadequate bladder drainage, abnormal bladder dynamics and high intravesical pressure which usually result in hydronephrosis and vesicouretral reflux (VUR) [1].

Among these factors also is the urinary tract infection (UTI) which constitutes a major threat to both the upper and lower urinary tracts. Owing to the particular nature of their bladders, those children are not capable of adequate bladder emptying which predisposes to bacterial inoculation of their lower urinary tract. This inoculation is facilitated by the lifelong clean intermittent catheterisation (CIC) used for bladder emptying [2].

Bacterial inoculation of the lower urinary tract is manifested by persistent asymptomatic bacteriuria, and repeated lower and upper urinary tract infections. Such repeated infections may result in many complications including development of renal and vesical calculi, alteration of the level of continence and renal scarring ending by renal failure [3].

Actually, UTI in such children has a great morbidity as well as mortality and should be diagnosed early and treated promptly; otherwise, it will result in serious complications in both the upper and lower urinary tracts. For this reason a strong background and a solid knowledge concerning the epidemiology, risk factors, diagnosis, complications and treatment of UTI in such children is mandatory for those involved in the care of this group of children. Herein, we display the different forms of UTI in such a subset of patients, their diagnosis, prevention and treatment.

38.2
Asymptomatic Bacteriuria

Schlager et al. defined bacteriuria as the presence of $\geq 10^4$ colony forming units per millilitre in a collected urine specimen by CIC [1]. Many factors predisposed to the development of such asymptomatic bacteriuria including mainly the incomplete bladder emptying, use of CIC, and constipation which constitutes a major problem predisposing for asymptomatic as well as symptomatic UTI [1].

The exact mechanism of the chronic bacterial inoculation in such children is not well known; however, it is proposed by Schlager et al. that the motile bacteria coming from the gastrointestinal tract and present in the perineum may have access to the bladder by the use of CIC. Since CIC is a lifelong act in those children, chronic bladder inoculation by such organisms is established [1].

Different organisms have been implicated in asymptomatic bacteriuria. In the study by Schlager et al. 70% of the studied cultures isolated weekly from 14 children with neurogenic bladder were positive. Of these cultures, 88% showed the usual pathogens including predominantly *Escherichia coli* and *Klebsiella*; the remaining 12% showed coagulase-negative staphylococci and

Corynebacterium spp. as the predominant commensal organisms [1].

This asymptomatic bacteriuria raised many questions: Will it result in symptomatic UTI? Is it associated with increased risk of pyelonephritis? Is it associated with a risk of development of renal scars without true UTI?

Controlled studies were performed to study the effect of antimicrobial prophylaxis in eliminating this asymptomatic bacteriuria and in reducing risk of the development of symptomatic UTI. Among these studies are the studies by Duffy and Smith [4] of 28 men and 3 women with neurogenic bladder using nitrofurantoin as a prophylactic antimicrobial agent, and the study by Mohler et al. [5] of 36 men and 8 women with neurogenic bladder using trimethoprim-sulphamethoxazole in prophylaxis.

The previously mentioned studies concluded that the chronic use of antimicrobial prophylaxis in this group of patients results in emergence of highly resistant bacterial strains. These bacterial strains are capable of producing severe UTI resistant to antimicrobial therapy [4, 5].

In parallel to these studies, Schlager et al. tried nitrofurantoin prophylaxis against placebo in a double-blind placebo-controlled crossover study over 15 children with neurogenic bladder. They proved that the use of nitrofurantoin prophylaxis in such children exposes the child to the drawbacks of prolonged antibiotic use without a significant benefit. The use of nitrofurantoin decreases the incidence of UTI related to *Escherichia coli*, but it leads to the development of another type of virulent bacteria, namely *Klebsiella* and *Pseudomonas*. This increases the risk of UTI with resistant organisms and also its use does not eradicate completely the bacteriuria in such children [6].

Whether or not bacteriuria is capable of producing renal scars, Ottolini et al. [7], who studied this, concluded that asymptomatic bacteriuria alone, without VUR, is not a cause for renal scars in children with neurogenic bladder. As a result, trials aimed at the eradication of asymptomatic bacteriuria by antibiotic prophylaxis are not justified in children with no VUR [7].

In a trial for controlling bacteriuria in children with neurogenic bladder, Schlager et al. studied the effect of using a single sterile catheter for each void in children committed to CIC. They compared this to the effect of using the same catheter several times, but they found no difference concerning the level of bacteriuria between the two groups. In conclusion, CIC with a single sterile catheter in each void is not a suggested method to reduce bacteriuria and to prevent UTI, as would be expected [8].

38.3
Urinary Tract Infection in Children with Neuropathic Bladder

Chronic and recurrent UTI in children with neuropathic bladder constitutes a major risk for those children. This repeated UTI means very high morbidity associated with frequent hospitalisation and increased costs of treatment; moreover, the increased hospitalisation creates a potential risk of acquiring nosocomial UTI with multiresistant organisms [9].

38.3.1
Risk Factors of UTI in Neurogenic Bladder

Many factors play a role in the recurrent UTI in children with neurogenic bladder including, firstly, the inability to empty their bladders completely. This is the result of the non-coordination between the detrusor and the external urethral sphincter. This results in three deleterious events, namely the high voiding pressure, increased amount of post-void residual urine and the inability to wash properly the urethra from the commensal bacteria [10].

The persistent bacteriuria is a major risk factor for the development of chronic as well as recurrent UTI, especially in the absence of adequate voiding of the bladder and the presence of VUR [11].

One of the most important risk factors for the development of febrile UTI is the presence of reflux, which facilitates the ascent of the bacteria from the bladder to the upper urinary tract with the refluxing urine as well as facilitating the transmission of the high intravesical pressure inside the bladder to the kidney, increasing the possibility of pyelonephritis [11].

Moreover, the repeated use of antibiotics for treating the UTI or as a prophylaxis against UTI results in the development of multiresistant organisms which are capable of producing severe forms of urinary tract infection. The age of the child has been considered as a risk factor for the development of UTI. The incidence of UTI increases with the age of the child reflecting the interplay between the previous factors including bacteriuria, development of multi-resistant strains and the evolution of the neuro-urological status [11].

The presence of untreated constipation represents another risk factor for the urinary tract infection, since it is a major source for the pathogens involved in the pathogenesis of UTI. It reduces the functional bladder capacity and the reservoir function of the bladder, and it should always be detected and treated promptly to decrease the frequency of UTI [12].

In the study by Vaidyanathan et al. on patients with neurogenic bladder caused by spinal injuries, they found that the method of bladder drainage used was a major factor in determining the incidence of UTI. Clean intermittent catheterization was associated with the least number of infectious complications compared with the use of indwelling catheters [12].

38.4
Diagnosis of UTI in Children with Neurogenic Bladder

Diagnosis of UTI in children with neurogenic voiding dysfunction is difficult owing to the presence of considerable bacteriuria and pyuria. Moreover, the presence of neurological sensory deficit makes the child unable to detect symptoms of lower UTI, including the dysuria which could be detected by a normal child [6].

For the above-mentioned reasons symptomatic UTI in such children is diagnosed according to the parameters set in the round-table discussion of symptoms of UTI in neurogenic bladder, at the October 1990 meeting of the American Academy for Cerebral Palsy and Developmental Medicine, in Orlando, Florida. These guidelines defined UTI as a positive urine culture with fever, abdominal pain, change in continence pattern, or change in colour or odour of urine [2]. Consequently, we have two types of UTI, namely lower UTI with no fever, and upper UTI with fever, malaise, lethargy and abdominal pain.

38.5
Infectious Complications in Children with Neurogenic Bladder

Renal insufficiency and chronic renal failure is the endpoint complication of repeated pyelonephritis which is not treated effectively. Every time they have acute pyelonephritis, their kidneys are liable to develop new parenchymal scars, decreasing the number of functioning nephrons [10].

Saurerwein et al. [10] and Vaidyanathan et al. [12] showed development of infectious stones, especially in those who have bladder augmentation. Moreover, they found that the use of indwelling catheters increases the incidence of local infectious complications including periurethral abscess, recurrent urethritis, prostatitis, epidydimitis and epididimo-orchitis. Moreover, it increases the incidence of infectious stones in the bladder.

Cheang et al. reported the development of septicaemia secondary to undrained infected urinary tract and a state of hyperammonaemia and hyperammoniacal encephalopathy secondary to lower urinary tract infection in a child with neurogenic bladder. In this child the bladder was not drained efficiently, resulting in ammoniacal intoxication and hyperammonaemia [13].

Investigations of UTI in such children include laboratory as well as radiological investigations [14, 15].

38.5.1
Laboratory Investigations

38.5.1.1
Urine Sample and Culture

Urine sample and culture aims at detection of significant bacteriuria and pyuria, as well as determining the type of the organism and its antibiotic sensitivity for being a guide to the treatment. Urine specimen can be taken by various means, including CIC in patients dependent on CIC for bladder emptying, and suprapubic puncture.

38.5.1.2
Blood Picture and Blood Chemistry

Blood picture includes the total and differential leucocyte counts for early detection of septic states and for monitoring the evolution of the patient during the course of the treatment.

Blood chemistry includes serum urea and creatinine to evaluate renal function. C-reactive protein is a good indicator of bacterial infection and is used also as a marker for follow-up of the patient during treatment.

38.5.2
Imaging

38.5.2.1
Renal and Bladder Ultrasound

Renal and bladder ultrasound is non-invasive test, simple and easy to yield information concerning the renal parenchyma, the degree of hydronephrosis and the presence of any stones whether in the bladder or in the upper urinary tract.

38.5.2.2
Cystography

Cystography is not recommended during the period of active UTI and should be performed after the adequate treatment of acute UTI. It can diagnose VUR as a predisposing factor for febrile UTI in those children.

38.5.2.3
Renal Scan

The DMSA scan has a role in the period of acute UTI since it can diagnose acute pyelonephritis by generalised decrease in the uptake of the radiotracer by the kidney with absence of reduction in the total volume of the kidney compared with the other side and with previous imaging. It can be used also to know the sequel of febrile UTI and to diagnose the development of new scars in the kidney [15].

38.5.2.3
Urodynamic Studies

Urodynamic studies are performed in the presence of repeated lower UTI or upper UTI for diagnosing bladder instability and any change in the intravesical pressure predisposing to recurrent UTI.

38.6
Prevention and Treatment of UTI in Children with Neurogenic Bladder

Many options have been suggested to reduce the bacteriuria and to minimize the incidence of symptomatic UTI including prophylactic antibiotics, intravesical instillation of antibiotics, use of sterile catheters and the single use of sterile catheter for CIC [8]; however, all these trials were proved to be inefficient in reducing UTI, and even the use of prophylactic antibiotics or the intravesical instillation is associated with the selection of more resistant and virulent bacteria capable of producing severe UTI.

Moreover, the previously mentioned studies proved that the use of single or sterile catheter does not reduce the incidence of bacteriuria, and hence the optimum methods for protecting against UTI in those children is the proper bladder emptying which should be emphasized on regular intervals. The use of prophylactic antibiotics is indicated only in patients having concomitant reflux for minimising the incidence of pyelonephritis [6, 8].

Proper hygiene and management of chronic constipation in those children is important in preventing UTI; hence, fecalomas represent a major source for the bacteria causing UTI and also affects the reservoir function of the bladder [6].

The use of indwelling suprapubic or urethral catheters is absolutely contraindicated in those children because of the high number of infectious complications associated with this use, and instead we can use the clean CIC as an effective and safe measure for evacuating the bladder [14].

Despite the previous measures to prevent UTI in children with neurogenic bladder, we may encounter lower or upper UTI necessitating prompt treatment depending on the accurate and rapid diagnosis based on the results of urine and blood examination.

The UTI in those children is confirmed by the presence of more than 100,000/ml leucocytes in the urine sample and the presence of more than 100,000/ml of bacteria in urine culture whether associated or not with symptoms. We have to give the proper antibiotic therapy based on the culture and sensitivity, and for the proper time, to eradicate completely the UTI and to guard against the chronicity of the infection [10].

Finally, for the prompt treatment of such infectious complications, we have to distinguish between lower UTI and upper UTI. For lower UTI, culture and sensitivity determine the proper antimicrobial agent to be used, which should be given for a sufficient period of about 7 days in a sufficient dose to eradicate the infection and to prevent recurrence [16].

In the case of recurrent lower UTI, we have to fully eliminate the presence of a predisposing factor, such as constipation, bladder instability or vesical stones. Full clinical examination to detect fecalomas, together with proper imaging and urodynamic studies, help in diagnosing efficiently these predisposing factors. Constipation should be treated carefully, whether by dietary regimens, mild laxatives or even enemas. Treatment of constipation aids in alleviating recurrent lower UTI [17].

The presence of bladder instability should be treated by anticholinergics to reduce the pressure inside the bladder coupled with regular emptying of the bladder using CIC [17]. Bladder stones should be treated radically with removal of the whole stone without fragmentation to avoid any residual nuclei for new stone formation, especially in augmented bladders.

In case of upper UTI, the treatment should be more prolonged and rapid to guard against renal scarring. We then have to investigate the child carefully using ultrasound abdomen and pelvis, cystography and urodynamic testing to diagnose any predisposing factor such as the previously mentioned factors, in addition to VUR, which should be treated efficiently to prevent recurrent febrile UTI, which is hazardous for the renal function.

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Bladder Calculi in the Pediatric Augmented Bladder: Risk Factors and Prevention Strategies

39

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39.1
Introduction

Enterocystoplasty, first described in 1899 [34], is even more an essential tool in the treatment of dysfunctional bladders due to spinal cord dysraphism, posterior urethral valves, bladder exstrophy, other congenital disorders and malignancy.

By the end of the first century of bladder augmentation procedures, the awareness of the related postoperative problems has considerably increased.

Waiting for new surgical approaches coming from the development of tissue engineering techniques, pediatric urologists must face again the well-known, potentially potential and significant complications of enterocystoplasty, such as bladder stones, urinary tract infections (UTI), neoplastic progression, spontaneous perforation, and metabolic disorders which require an imperative lifelong watchfulness and preventive measures.

Bladder stone formation is a serious complication and its incidence varies between 3 and 52% according to a review of recent literature [4, 22, 28, 35, 37], with the majority of calculi being composed of struvite or calcium/apatite.

Looking at the incidence of urolithiasis in the largest reported series on augmented bladders in children, the results are varied, unlike that of the adult population which shows a lower frequency [31, 42]: Nurse et al. reported 42 cases of stone formation in 467 patients (9%) [36]; Kaefer et al. 32 cases in 207 patients (15%) [25]; Kronner et al. 29 cases in 286 patients (10%) [28]; DeFoor et al. 12 cases in 105 patients (11%) [11]; and Hendren and Hendren reported 23 cases in 129 patients (18%) [22]. Blyth et al., in a report on 87 children and young adults, had a bladder stone rate as high as 30% in 26 patients affected [4], and Palmer et al. reported 52% [37], observing 26 patients with stones in 49 augmented cases.

The mean post-operative time to stone formation, according to various authors, is shown in Table 1.

Patients with bladder calculi can be symptom free, having had the diagnosis incidentally made during ultrasound follow-up, but sometimes the clinical consequences of the lithiasis are so serious as to make children very ill: pyelonephritis, UTI, and even death have been reported in two large series [4, 37].

39.2
Risk Factors

Several etiological factors affecting the incidence have been identified. Their effective load is not clear yet and some “weak points” still need to be carefully studied.

The risk factors that must be taken into consideration are:

1. Bowel segment used, type of reservoir, and associated procedures to improve continence (urinary stasis)
2. Urinary tract infections and persistent bacteriuria
3. Mucus production caused by the augmented enteric segment
4. Metabolic disorder
5. Foreign bodies (surgical sutures employed).

In addition, there are some predisposing conditions that must be kept in mind, such as immobility in wheelchair children, who need self-catheterization with easily incomplete drainage of urine, or poor compliance of the children and their family towards post-operative management, which could determine the quality of the result.

Besides these, we also have to remember the usual contributory factors in standard stone formation, such as dietary excess in terms of animal protein and purine,

Table 1. Stone incidence in intestinal bowel augmentation. *N/A* not applicable

Reference	Number	Mean follow-up	Stone incidence (%)	Mean time to stone formation (range)
[18]	383	Minimum 3 years	16.7	36 months (N/A)
[4]	87	Minimum 1 years	30	24.2 months (3–75 months)
[37]	40	4 years (9 months to 9 years)	52.5	24.5 months (2–72 months)
[36]	467	Minimum 3 years	9	N/A (6 months to 11 years)
[43]	126	Minimum 3 years	30	43.1 months (N/A)
[25]	207	5.1 years	15	3.6 years (0.5–8.6 years)
[28]	286	Minimum 2 years	10	68 months (12–183 months)
[5]	60	5.2 years	11.6	35 months (13–59 months)
[32]	89	4.9 years	16	39 months
[3]	158	Minimum ca. 18 months	9	43 months (3–132 months)
[44]	148	3.3 years	15.7	45 months (1–120 months)
[11]	105	8.4 years (2–15 years)	11	5.2 years (1.4–14 years)

calcium, oxalate, sodium, and low intakes of fluid, fibres, and magnesium [45].

Race, gender, and aetiology of bladder dysfunction do not significantly influence the incidence of urolithiasis [37].

We consider all risk factors singularly, even if, to our knowledge, they act together in a multifactorial manner.

39.2.1
Bowel Segment Used, Type of Reservoir, and Procedures for Continence

The choice of the intestinal segment to augment the bladder capacity depends on a number of structural and metabolic factors well described by Kaefer et al. [26], in addition to the surgeon's preference due to previous experience.

The great difference in bladder stone formation rate is between the use of stomach or ileum and colon for reconstruction.

Gastrocystoplasty, which seems to be a very attractive solution, especially in cases of chronic renal failure, has a very little lithogenic effect, because of the lower mucus production, the ability of gastric secretion to acidify the urine, and the consequent decreased number of UTI. The bladder stone incidence in gastric replacement is very low in all reported series. Kronner et al. did not find any stones at all on follow-up of 37 patients [28]. Kaefer et al. reported only two cases in a series of 70 patients [25], vs 30 of 137 patients augmented with other intestinal segments. The latter authors reported also a case of a uric acid calculus and pointed out the role of the acidic urine in potentiate uric acid precipitation and stone formation.

Garzotto et al. first published a similar case in gastrocystoplasty in 1995 [15].

Recently, DeFoor et al., in their own experience of 105 patients, compared the frequency of bladder stones between those who had bladder augmented with stomach and those with ileum or colon [11]. Their stone rate of 11% is similar to the rate in series that have included a higher percentage of gastric augments. Looking at the 37 ileum and the 18 colon-augmented patients they found, respectively, 26 and 6% of stone formers, whereas only 2% of 50 gastrocystoplasty patients.

The recurrence rate on all of them was 33%. Considering the complication of urolithiasis as the sole issue, the gastric segment could be the best tissue for bladder reconstruction. Surprisingly, the observations of hematuria–dysuria syndrome, and the spontaneous perforation due to peptic ulcer and metabolic alkalosis, due to the excretion of hydrogen and chloride ions, limits its use, which is much more recommended in cases of short bowel syndrome, as in cloacal extrophy, or in cases of previous bowel irradiation [1, 33, 41].

Lithogenic property of ileum and colon are both linked to heavy mucus production and increased risk of UTI, due to chronic bacterial colonization by urease-splitting organism (see below) [4]; however, mucus production from the ileum is less than from colon as Rink and Adams point out [40]. These authors, and also Hendren and Hendren, confirmed clinically this data [22].

The other advantage of ileum is that mucus production appears to decrease with time following ileocystoplasty, presumably from villus atrophy. This change does not happen in the colon, whose absorbable mucosa continues to secrete lifelong significant quantities of mucus [29].

Despite these considerations, the difference in lithogenic ability between ileo and colonocystoplasties is not

Table 2. Stone incidence related to surgical procedures. *BNS* bladder neck surgery, *WS* wall stoma, *RR* relative risk

Reference	Bladder augmentation (%)	Bladder augmentation + continent diversion (%)	RR
[4]	20.8	33.3 (WS)	1.6
[36]	6	21	3.6
[25]	13.3	21 (WS) 14.7 (BNS)	1.6 2.45
[28]	6	14.3 (WS) 21.1 (BNS + WS)	2.38 3.51
[5]	7	17	2.43
[32]	6.8	24.4 (BNS)	3.59
[3]	8	10.3 (WS)	1.28
[11]	11	18 (WS) 22 (BNS)	1.64 2

as high as between these and gastrocystoplasty. Hendren and Hendren [22], in their series, reported quite the same incidence for sigmoid and ileal augmentation: 6 and 10%, respectively.

The wide variability in the literature of the rate of the stones depends not only on the intestinal tract used, but also on the type of bladder reconstruction and on the emptying modality used. These two factors have a great influence on the ability to wash out the augmented bladder and on related urinary stasis.

It is well known that continent reservoirs associated with the Mitrofanoff channel are at greater risk of stone formation than the augmented bladder emptying through the urethra (Table 2). In fact, when urine drains from the base of the reservoir, stones are less easily formed, whereas the drainage from the top of the bladder greatly increases the possibility of calculi [25, 45].

Stone rate, in series that include more continent reservoirs, is in fact much higher as reported by Blyth et al. [4] and Palmer et al. [37]. Blyth et al.'s patients had undergone sigmoid colocystoplasty and almost half emptied through a Mitrofanoff conduit.

Nurse et al. [36], in a large series of 467 ileum and colon-augmented bladders, pointed out these arguments looking at their experience regarding the difference between continent diversions and orthotopic cystoplasties, emptying with or without clean intermittent self-catheterization (CISC). They found a total of 42 stone cases (9%) developed from 6 months to 11 years after reconstruction. The stones were three times more common in patients with continent diversions than in those with orthotopic cystoplasties and, inside the latter group, five times more common in patients who voided by CISC than in those who voided spontaneously.

In addition, all bladder neck procedures that increase the continence, such as Salle, Young-Dees-Laedbetter, and Kropp procedures, or reconstruction operations as well as sling and artificial urinary sphincters, cause urinary stasis within the bladder. Kronner et al. evaluated the stone incidence in their 286 augmented patients, related to different approaches, and they found a 6% incidence after only enterocystoplasty [28], 14.7% after augmentation plus bladder neck procedures, 14.3 % for augmentation plus catheterizable stoma, and 21% after augmentation, bladder neck procedures, and stoma. Mathoera et al. report the same high percentage of stones in 45 of 89 patients treated with bladder outlet resistance surgery who showed 24.4% of calculi [32].

The stone recurrence rate after removal is affected by the same risk factors considered for the first calculi as well as the extraction procedures used, and it also depends on the length of the follow-up. Barroso et al. observed a high rate of stone recurrence (32%) [3], especially in patients with enterocystoplasty without a wall stoma. They suggest prevention of stone recurrence in patients using CISC. Other authors, such as Palmer et al., report a lower rate of recurrence (17%) [37, 38], that may be due to a shorter follow-up. With regard to the best approach for avoiding stone recurrence, few authors do not find a statistically significant difference between open cystolythotomy and endoscopic techniques [25, 28, 34], even if they report a lower recurrence rate in open treatment (see below).

39.2.2
Urinary Tract Infection and Bacteriuria

Persistent bacteriuria in enterocystoplasties due to intermittent catheterization, urinary stasis, and mucus in the reservoirs is unavoidable, and in most patients it is difficult or impossible to keep sterile urine by antibiotic prophylaxis [30].

Infection seems generally accepted to be the most common etiological factor in lithogenesis [37]: this is supported by the evidence that stones developing in augmented bladder are principally made of triple phosphates, with varying concentration of apatite (i.e., calcium and fluorine phosphate), struvite (i.e., magnesium ammonium phosphate), and ammonium urate, implying that bacterial colonization with urease producing organisms is a leading cause [4, 20]; however, according to Nurse et al. bacteriuria is not the most important factor in the aetiology of the stones [36], because they find that infected urine is also present in 75% of patients not forming stones. They support that UTI seems to be a consequence of stone formation rather than a cause of it.

In any case, as postulated by Blyth et al. [4], the urea-splitting intestinal bacteriae, such as Proteus, Providencia, and Klebsiella species [9], produce urease that catalyze the breakdown of urea to free ammonium and carbon dioxide, which results in an alkaline urine. The alkalization increases the phosphate ion concentration through the dissociation of hydrogen phosphate. As a consequence of these reactions, urine may be supersaturated with respect to calcium phosphate (at pH 6.6) and struvite (at pH 7.2), resulting in crystal formation. Due to the lower pH that calcium phosphate needs to precipitate, it is the first salt to crystallize: as it is expected that most of the stones in augmented bladder contained more calcium phosphate than struvite (44 vs 34% by Palmer et al. [37]) [4, 11, 45], even if some authors report that the majority of stones are struvite, Mathoera et al. find that ammonium urate and calcium apatite only occurred secondary to struvite stones [25, 28, 32].

The different bowel segments used for augmentation had no effect on incidence of stone formation due to persistent bacteriuria, except for the stomach. Gastrocystoplasty has definite advantages in that it secretes less mucus and, by the gastric mucosa secretion of acid, which decreases urine pH, inhibits bacterial growth and prevents the basic milieu that allows struvite stones to develop [28]; however, Palmer et al. observed that in ileocystoplasties stones are primarily of struvite [37], whereas in the ileocecocystoplasties they are of apatite and ammonium urate, and in sigmoidocystoplasties the main components are apatite and struvite.

39.2.3
Mucus Production

Retention of mucus appears to have an important role in the genesis of the bladder stones in patients with bladder augmentation, in association with bacteriuria and urinary stasis. It enhances lithogenesis directly by acting as a heterogeneous nidus or indirectly by facilitating bacterial colonization of augmented bladders and retention of triple phosphates in it [32].

Patients in whom stones formed have a significantly higher calcium-to-phosphate ratio in the mucus than similar non-stone-forming patients [27].

Intestinal mucus is composed of carbohydrate rich glycoprotein (mucin) from 1 to 10%, and in their studies Forstner and Forstner showed that calcium has a high affinity for mucin [4, 20]. They also demonstrated that binding of calcium to the calcium binding sites on this glycoprotein leads to mucin infolding and loss of water from within itself; thus, more compact, dense, and insoluble mucine becomes a nidus for crystallization.

This role of mucus is also suggested by the small stones sometimes evacuated that seem to be a spectrum of material from mucus through a chalk-like material to frank stone [27]. Furthermore, the presence of a viscous fluid containing similar high calcium-to-phosphate ratios and high concentration of calcium, phosphate and magnesium, in the centre of bladder stones, confirms that intestinal mucus acts as a nidus for stone formation; therefore, Khoury et al. believe that calcium-to-phosphate ratios may have great predictive value in studies of urolithogenesis [27]: mucus from patients with augmentation should be evaluated for urinary constituents, such as calcium, phosphate and magnesium.

Mucus can also cause significant morbidity, in addition to its postulated lithogenic property, by promoting urinary stasis and recurrent UTIs. It may serve as a biofilm leading to a protected environment for pathogenic bacteria [6]. By harbouring organisms mucus predisposes to recurrent UTIs.

Mucus can also impede bladder emptying by blocking the small-calibre catheters used for intermittent catheterization, leading to incomplete emptying, increasing the risk of infection and also leading to perforation [21].

In the unusual cases of stones that develop in the upper urinary tract after enterocystoplasties, it seems that vesicoureteral reflux (VUR) allow mucus to reach the renal pelvis and remain entrapped in it, acting as a nidus for stone formation. Consequently, it is important to prevent VUR in patients who have undergone bladder augmentation [36].

On the other hand, it must be outlined that the presence of an intact mucosal layer is important in protecting intestinal mucosa from urinary carcinogens and other urinary contents, when bowel is incorporated into the urinary tract [36].

Gastrocystoplasty produces less mucus and does not absorb free water, so supersaturation of urinary solutes while urine is present in the reservoir may be less likely than with absorptive intestinal segment.

39.2.4
Metabolic Factors

The metabolic factors that lead to stone formation are numerous and include risk factors for lithogenesis peculiar to patients with enterocystoplasties besides other common risk factors for crystal formation.

A metabolic aetiology for stone formation after bladder augmentation includes hypocitraturia (citrate is a protective inhibitor against the crystallisation of calcium phosphate in urine) due to the tendency for UTI and to a low intake of potassium [37], and hyperoxaluria, secondary to the removal of small bowel and to the chronic antibiotic therapy that knocked down the gut flora that metabolizes oxalate.

The other common metabolic risk factors are: hyperuricosuria, caused by dietary excess in terms of animal protein and purine; hypercalciuria, low urinary magnesium excretion, because of a low magnesium intake; and low urine volume secondary to a low fluid intake [45].

39.2.5
Foreign Bodies

Several foreign bodies, such as metal surgical staples or absorbable staples, have been implicated as a source of chronic infection and as a nidus for stone formation after bladder augmentation. Metal staples were found interposed between the bladder mucosa and the calculus. Palmer et al. also found an association between absorbable staples and calculogenesis [37]: in each case a ghost of the staples is found within the calculus mass. They also found that the former is more likely to contain apatite. Consequently, they asserted that use of the staples had to be abandoned and suggested the use of a running absorbable suture to reapproximate reconfigured bowel segments in enterocystoplasties.

Blyth et al. moreover reported that one of the most common causes of stone formation that he has seen in his postpubertal patients has was due to hair serving as a nidus [4], probably due to CISC.

39.3
Prevention Strategies

The prophylactic treatments in this group of patients are not yet clear, because of the different outcomes and experiences of the various authors. The main purpose of the prophylaxis is to avoid urine and mucus stasis to reduce the incidence of bacteriuria.

Woodhouse et al. claim that improving the fluid intake, not less than 2.5 l/day [45], is a prerequisite to treat these patients, because it is possible that a continuous flow helps to wash out bacteria and decrease the accumulation of lithogenic mucus [25]. Mathoera et al. point out that this approach is not effective when voiding is carried out by CISC [32].

Above all, to reduce urinary stasis or mucus retention diligent catheterization with a complete bladder emptying and irrigation is essential. The regular complete emptying of the bladder by spontaneous voiding seems to reduce the risk of stone formation when compared with emptying by CISC [36]; however, stone formation does not occur in any of the children performing CISC upon their native bladders, implying that this alone does not predispose the child to calculi [5].

Clearly, patients attempting to drain their bladder through a stoma located on the abdomen have a greater likelihood of leaving residual urine and mucus in the bladder floor and hence increase their risk of stone formation (a 60% higher rate of stone formation, as reported by Kaefer et al. and Blyth et al. [4, 25]) [5, 26, 36].

To avoid mucus and urine stasis, some authors also suggest an early regimen of regular bladder irrigation, with saline solution [11, 25] or with antibiotic solution in persistent bacteriuria [25]. Many Authors stress the importance of daily irrigation in order to achieve excellent results [23, 25, 28, 32, 39].

On the contrary, Brough et al. conclude that bladder washout does not significantly reduce the lithogenesis [5], even if their protocol is to wash out the neobladder on a weekly basis. The bladder washout has to be continued indefinitely in patients who depend on CISC [25].

Antibiotic prophylaxis against UTI is only recommended in patients with VUR or recurring UTIs, because it may increase their risk of hyperoxaluria, as mentioned above. To inhibit the urease reaction Blyth et al. suggest acetohydroxamic acid therapy [4].

To reduce the production of mucus George et al. proposed oral Ranitidine [16]. Gillon et al. suggested the mucus washout of the bladder with acetyle cysteine [17].

Against the metabolic factors, a consistently high fluid intake is a prerequisite for the management of these children, so as to minimise salt and salty food in order to reduce the risk of hypercalciuria. To reduce hyperoxaluria they have to keep to a minimum their intake of high oxalate-containing foods (spinach, soy products, butter, chocolate, etc.) [45].

To avoid hypocitraturia it is mandatory to increase the intake of potassium, or to treat these patients with oral potassium citrate therapy [39].

Finally, they should follow a well-balanced diet with more fruit, vegetables, brown bread, fibres, magnesium, etc.

39.4
Treatment Options

Once stones have been formed in the augmented bladder, the treatment strategies include open cystolithotomy, endoscopic cystolitholapaxy and percutaneous cystolithotomy; the latter can be associated to lithotripsy to reduce the stone size.

The therapeutic approach must certainly be tailored to the specific anatomical requirements of the patient. The choice of the best option for stone removal depends on several factors including calculi size, hardness, number and location, ability to pass the urethra due to previous surgery, conduit available to reach them and type of bladder reservoir.

For large stones open cystolithotomy is indicated to extract intact stones without leaving residuals, even if the dissection may be difficult sometimes.

Mechanical stone disintegration before surgery is considered time-consuming and complicated by a large number of little fragments that are difficult to remove and that can easily lead to a recurrence. It is well known that infectious stones rapidly accumulate again if they are not completely eliminated [25, 45].

Palmer et al. always advocated endoscopic evaluation before open surgery [38], to estimate the stones' load and to decide the optimal treatment. They reported the higher incidence of 21 stone formers in 40 augmented patients (52%), half of the cases with a continent diversion, with 4 cases of recurrences. They treated 18 of 25 cases (72%) cystoscopically using electrohydraulic lithotripsy or simple extraction.

The endoscopic cystolitholapaxy is an important tool in extracting stones. The advantages of this procedure is to avoid open surgery through an abdomen scarred by previous surgery and to decrease patient morbidity in terms of hospital stay and discomfort. Moreover, in some series there has been no statistically significant difference in stone recurrence rate between open and endoscopic management [7, 28, 38]. Kaefer et al. strongly supported this management since they treated 50% of their patients endoscopically and 50% with open surgery without any significant difference in recurrence rate (2% in both groups) [25].

Even Nurse et al. in their experience of 42 stones cases in 407 augmented bladders chose the endoscopic technique in 22 of 25 patients with an orthotopic cystoplasty with good results [36], whereas they performed percutaneous approach in 14 patients with continent diversion.

The type of the conduit to emptying the bladder considerably affects the endoscopic stone removal. If the conduit is the natural urethra, cystolitholapaxy can be used [45], although the necessary dilatation and manipulation can make the continence worse, especially when depending on the bladder neck reconstruction, as in extrophy.

Most authors point out that the endoscopic procedures are safe and effective in the majority of cases, although sometimes they can be unsatisfactory, because the fragments embedded in the mucosa are difficult to clear, especially when the contour of the augmented bladder is abnormal or there are some diverticula difficult to reach properly with the instruments [25, 45].

The access via a continent abdominal stoma is not always feasible, and attention must be maintained in order to avoid the disruption of the continence mechanism. The Mitrofanoff channel is often too narrow and will only accept a pediatric or flexible cystoscope.

Woodhouse et al. were able to disintegrate and to clear small stones with a flexible cystoscope and a laser fibre lithotripsy [45], although they observed that the field of view is small and it can be difficult to ensure that all fragments are cleared.

It is much easier in fact to obtain endoscopic stone removal from an orthotopic than from a continent bladder reservoir [36].

When the endoscopic access is unavailable or its use is believed dangerous for continence, some authors suggest percutaneous stone extraction to reduce the morbidity associated with open surgery [7, 12, 24, 45]. This approach was first described by Gopalakrishnan et al. and by Ikari et al. in children with stones in normal bladders, and subsequently it was also applied to children with augmented bladders [7, 19, 24].

Cain et al. strongly suggest, as a key element, the suprapubic skin incision on the exit site of the tube draining the initial bladder augmentation to enter the full bladder with an angiocatheter – under direct cystoscopic guidance through either the urethra or the cutaneous stoma – and then to start the progressive dilatations until a 24- to 30-F sheath is placed [7]. This access allows the tube to be passed through the bladder wall, where usually the bladder is secured to the posterior fascia at the time of the augmentation, obviating the risk of damaging the bowel and the blood supply of the reconstructed bladder. The stones are removed with a stone basket or grasping forceps, sometimes with a previous lithotripsy if the size is too large. This technique, recently reported also by Woodhouse et al. in 15 patients without complications [45], was considered safe and less morbid than open surgery by Docimo et al. [12] who, comparing the two approaches, did not find any significant differences between them.

An alternative treatment to surgery was proposed by Blyth et al. [4], who reported a dissolution of calculi with a protocol of daily irrigation by 30 cc of 10% hemiacidrin for a 3–6 months period. This treatment was successful in 7 of 17 patients, but 3 of them showed recurrences within 1 year of discontinuation of the therapy. Hemiacidrin irrigation, however, can play a role in decreasing particles after definitive treatment.

The optimal treatment of bladder calculi in patients with bladder augmentation remains a controversial approach. The policy of daily irrigations to evacuate the mucus, the prevention and treatment of UTI, the careful observation of the metabolic status, and the routine imaging on follow-up of the augmented bladders, especially in patients with continent diversion, are strongly recommended. All of these prophylactic strategies prevent lithogenesis or at least permit an early detection of bladder calculi: this allows a less aggressive endoscopic procedure or a minimally invasive approach to remove stones.

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Neurologic Bladder Dysfunction: a Condition at Increased Risk of Bladder Malignancy?

40

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40.1
Introduction

Augmentation cystoplasty is an excellent method for increasing bladder capacity in patients with bladder dysfunction secondary to spinal dysraphism, extrophy or anatomical bladder outlet obstruction [2]. The use of various gastrointestinal segments as urinary conduits or substrate for urinary reservoir augmentation has benefited many individuals with urinary incontinence [10, 29]; however, when urinary and intestinal tissues are placed in direct contact, numerous complications may occur, ranging from electrolyte imbalance to initiation of malignancy [29]. Only a few studies have prospectively evaluated the potential for histological changes in either the intestinal or bladder mucosa secondary to augmentation cystoplasty [14, 20, 29].

Tumour development at the urointestinal anastomosis is a well-known and worldwide accepted late complication following bladder augmentation.

Since 1929, when Hammer first reported adenocarcinoma 10 years following vesicosigmoidostomy, less than 100 cases of malignancies after reterosigmoidostomy have been reported [2, 23]. Most tumours developed exactly at the urocolonic anastomosis site. The risk of colon cancer is estimated to be up to 477-fold higher than in the general population in the age group of 25–30 years and eightfold in the age group of 55–60 years [2, 10]. Another category of patients at increased risk for bladder tumours are those with spinal cord injury. Proposed risk factors in these patients include chronic infection, chronic indwelling catheters and bladder stones [14, 28].

40.2
Risk Factors

Several conditions represents a risk factor for malignancy in patients with neurological bladder dysfunctions.

40.2.1
Chronic Indwelling Catheter

Delnay et al. report a large series of spinal-cord-injured patients who underwent biopsy evaluation after chronic indwelling catheter use [6, 9]. They found at biopsies examination a spectrum of inflammatory and proliferative pathological conditions, which were predominantly inflammatory and squamous tissue [7]. These nonmalignant histological changes included those considered by some to be premalignant, namely keratinizing squamous metaplasia and cystitis glandularis [25, 29]. Squamous metaplasia is a common result of chronic bladder irritation or infection. The relation of squamous metaplasia –with or without keratinisation – to squamous cell carcinoma of the bladder is controversial [8, 19, 22]. Squamous metaplasia, especially the keratinizing variety, has been interpreted as potentially premalignant. Squamous metaplasia has been reported to become more prevalent as duration of inflammation or irritation increases. Kaufman et al. reported squamous metaplasia in 80% of patients catheterized for more than 10 years, compared with 42% catheterized for less than 10 years and 20% without long-term indwelling catheters [9, 19, 23]. Squamous metaplasia is commonly associated (17–25%) with squamous cell carcinoma of the bladder [6, 9]. Furthermore, long-term follow-up studies of vesical squamous metaplasia demonstrate that 15–28% of patients ultimately have carcinoma [7, 9]. Squamous metaplasia may represent a premalignant lesion or may be a sign of a continuing inflammatory insult that can eventually result in malignancy. This issue has yet to be resolved;

however, from a clinical perspective this distinction may be less important. The patient with squamous metaplasia on biopsy is at greater risk for bladder malignancy, and every effort should be made to eliminate ongoing causes of inflammation and provide prolonged surveillance [9, 22]. Spinal-cord-injured patients should be treated with clean intermittent catheterization when possible and bladder stones should be treated promptly when identified. Close follow-up of patients with squamous metaplasia, who often present with advanced disease, may enhance cancer detection and prolong survival [9].

40.2.2
Augmentation Cystoplasty

Augmentation cystoplasty is an excellent method for increasing bladder capacity in patients with bladder dysfunction; however, when urinary and intestinal tissues are placed in direct contact, numerous complications may occur, ranging from electrolyte imbalance to initiation of malignancy [22, 29]. Only a few studies have prospectively evaluated the potential for histological changes in either the intestinal or bladder mucosa following augmentation cystoplasty.

Factors that have been proposed as initiators or promoters of tumour formation in patients treated with enterocystoplasty include bowel mucus, bacteria, urinary stasis, pH changes, nitrosamines and various growth factors [2, 29]. The production of nitrosamines by gram-negative bacteria remains one of the most supported hypothesis [6, 7]; therefore, the permanent bacterial colonization that often exists in patients treated with colocystoplasty might be the most significant risk factor for malignancy in this population [29]. In case of gastrocystoplasty, the gastric mucosa seems to be more resistant to the formation of premalignant lesions, perhaps due to the lower incidence of bacterial colonization secondary to high acid production of the gastric segment [2, 19].

40.2.3
Bladder Stones

The incidence of stone formation in the colocystoplasty is about 50% [8, 29]. Stones may form despite the use of regular bladder irrigation and clean intermittent catheterization [29]. Stones represent an inflammatory condition for the bladder and may induce histological changes of the bladder mucosa. In addition, bladder stones are responsible for recurrent urinary tract infections (UTI), which may represent another risk factor for bladder malignancy.

Other exogenous and endogenous risk factors for cancer development are represented by smoking, age, hereditary disposition, and male gender [1, 29].

40.2.4
Clinical Data

Bladder augmentation achieved popularity in the 1950s primarily for contracted, tuberculous bladders [1, 3, 11]. Smith and Hardy reported one of the first cases of cancer associated with bladder augmentation in 1971 [13, 27]. A review of the literature in 1990 revealed 14 cases of malignancy following bladder augmentation [14, 27]. Currently, it seems that the incidence of cancer following bladder augmentation or in general after urinary diversions varies between 6 and 29% (mean 11%) [16, 21, 27]. The risk of developing cancer is estimated to range from 400 to 7000 times more than that of the general population [27].

Austin reviewed the world literature up to April 2003 via MEDLINE for secondary tumours in urinary diversions using isolated intestinal segments [2]. Up to April 2003, 81 tumours in conduits (18), cystoplasties (45), rectal bladders (5), neobladders (3), colonic pouches (6) and ileal ureter replacements (4) had been reported [2].

He found that the median latency period for the development of malignant tumours in urinary diversion using isolated intestinal segments, in patients operated on for benign disease, was 21.5 years (range 2–40 years), whereas for benign tumours it was 22 years (range 5–25 years) [2, 24, 27].

Analyzing Austin's data, it appears that eight ureterosigmoidostomies were performed for malignant disease, and in these cases the latency to develop a malignancy is shorter. The other 73 cases were carried out for benign diseases [2]. The statistical analysis of these 73 cases showed that 59 (80.8%) occurred in continent urinary reservoirs (cystoplasties, rectal/rectosigmoidal/ileocecal rectal bladders, colonic/ileal neobladders, pouches and ileal ureteral replacements) and only 14 (19.2%) had developed in wet diversions (conduits) [2]. Considering that conduits are much more often the site of surgery worldwide, the risk of tumour in conduits seems to be smaller than in continent diversions. This hypothesis has been confirmed by a recent study evaluating 645 patients who underwent different types of urinary diversions using only the ileum, and who were followed up for a mean of 17 years (range 4–32 years) [2, 3, 16]. Tumours developed in 0.3% of 350 ileal conduits, in 0.8% of 260 ileal ureteral replacements and in 5.5% of 55 ileocystoplasties [3, 16, 21]. This report concluded that ileocystoplasties are more vulnerable for cancer at the urointestinal anastomosis than conduits or ureteral replacements [2]; however, although no malignancy has been reported within the first 10 years following augmentation cystoplasty in the paediatric population, in the international literature no long-term prospective studies involving periodic mucosal biopsies have been performed to evaluate the presence of premalignant conditions [29]. Recently, Baydar reported two cases of bladder tumours after gastrocystoplasty 14 years after the intervention for bladder augmentation [4]. Stonehill reported that indwelling catheters continue to be a major risk factor in spinal-cord-injury patients and increase the risk of bladder tumours, most notably squamous cell carcinoma [28]. Bickel et al. identified three of eight patients as having indwelling catheters for longer than 8 years and found squamous cell carcinoma in two of them [2, 28]. Kaufman et al. noted eight patients with indwelling catheters and discovered squamous cell carcinoma in six of them [2, 28]. These findings and those of others show the relationship of squamous cell carcinoma with indwelling catheters, and the correlation of cancer with a history of bladder stones. A history of bladder stones is also statistically demonstrated to be a risk factor for bladder tumours in spinal-cord-injury patients [16, 21].

Presently, the most common indication for augmentation cystoplasty in children and adolescents is the neuropathic bladder; the majority have no other risk factors for bladder cancer, which is noteworthy because this unique population virtually eliminates confounding risks for bladder cancer, making it easier to establish augmentation as an independent risk factor [27]. According to the National Cancer Institute, some authors estimat the prevalence of bladder cancer to be less than 0.3% of the general population aged below 50 years [13, 27]; however the true incidence of cancer associated with augmentation cystoplasty cannot be determined until close surveillance with long-term follow-up is achieved [27].

40.3
Tumour Histology

Many clinical, histological and pathological similarities have been demonstrated between cancer in ureterosigmoidostomy, urinary diversions and augmentation cystoplasties [5]. The most common histology in ureterosigmoidostomy-associated cancer is adenocarcinoma which frequently originates in close proximity to the ureterocolonic anastomosis [7]. In addition, the latency period between ureterosigmoidostomy diversion and cancer diagnosis is approximately 25 years [9, 27]. Adenocarcinoma at the bladder–intestinal junction is the most common histology and location of augmentation cystoplasty associated carcinoma [5, 12, 25, 29]. Various histologies have been found, including adenocarcinoma (16 cases, 52%), transitional cell (12, 39%), squamous cell (2, 6%) and 1 each (3%) of sarcoma, oat cell, small cell and signet ring carcinoma [9, 25, 29]. The bladder–intestinal junction was the most common location in 19 of 31 cases [7, 27]. Tumours originating from the native bladder were encountered less frequently (5 of 31 cases) [7, 27]. The mean latency period from augmentation to diagnosis was 17 years. In three cases reported by Soergel et al., transitional cell carcinoma was the only histological type [27]. In this series location of tumour at the bladder-augmentation junction was seen in two cases, whereas the location could not be determined in the third case because of inflammation and necrosis [27].

Bladder cancer following augmentation cystoplasty is a recognized risk and should no longer be considered a chance occurrence. This procedure has only gained popularity within the past 25 years, which limits the statistical power of the data and is not supported by the results of long-term follow-up. A change in the indication for augmentation cystoplasty has also made analysis difficult. The majority of the literature is based on an older population with inherent risk factors, including associated medical problems and exposure to infectious and environmental agents. The most common indications for surgery in 31 cases of augmentation-related bladder cancer were contracted bladder secondary to tuberculous cystitis (18), chronic cystitis (4), schistosomal cystitis (2), severe bladder instability in an elderly patient (2), urethral stricture (2), traumatic quadriplegia (2) and cervical squamous cell cancer [7, 12, 27].

40.4
Discussion

Considering that the median latency period for developing malignant tumours in urinary diversion using isolated intestinal segments or in bladder augmentation operated on for benign disease is 21.5 years (range 2–40 years), this problem is rarely discovered in paediatric patients but mainly in young adults [4, 10, 15].

The tumour spectrum is quite large and related to the type of bladder augmentation or urinary diversion performed. Following ureterosigmoidostomy almost all tumours are adenomas or adenocarcinomas [17]; however, following diversion using isolated intestinal or gastric segments, about 25% of tumours were transitional cell carcinoma, squamous cell carcinoma, signet ring cell carcinoma, leiomyosarcoma or oat cell carcinoma, and about 75 % were adenomas and adenocarcinomas [2, 18].

The reasons for the different tumour spectrum in urinary diversions with and without a faeces/urine mixture is still unclear. The larger urointestinal border in cystoplasties could be responsible for tumour induction at the two epithelial sides [26]. Another explanation might be the more intensive contact of urine and its carcinogenic contents with the urointestinal anastomosis in isolated urinary diversions compared with ureterosigmoidostomies with a prompt mixture of urine and faeces throughout the whole colon [2, 26, 28]. A completely unique carcinogenesis different than the suspected adenoma–adenocarcinoma sequence in ureterosigmoidostomies is also possible. Nevertheless, all of these theories remain speculative [2]. Tumour location is also different. Tumours following ureterosigmoidostomy occur only at the urocolonic borderline, whereas tumours following urinary diversion via isolated gut segments also develop distant to the urointestinal anastomosis [10, 27].

Although the exact mechanism is still unclear, a number of theories of carcinogenesis following urinary diversion have been discussed in the literature; some of these have been discounted, whereas others have become generally accepted. There is strong evidence that this form of carcinogenesis is multi-factorial. Several groups have proven the carcinogenic effect of urine in animal studies by isolating active substances such as epidermal growth factor and transforming growth factor [7, 8].

Crissey presumed that hydrolytic urine enzymes activate faecal carcinogens with the highest concentration at the anastomosis, where faeces and urine are mixed [2, 26].

Stewart et al. found increased excretion of nitrosamines in patients following ureterosigmoidostomy, suggesting bacterially catalyzed nitrosamine formation from secondary amines in faeces and bacterially reduced urinary nitrate [2, 15].

Kaolble et al. confirmed these results in humans, but none of the nitrosamines proved to be colon carcinogenic [2, 10]. Another theory which seems to have at least a role in tumour genesis following urinary diversion is associated with histological findings in intestinal segments used for diversion of chronic inflammation, especially with lymphoplasmatic infiltration and an increased number of eosinophil cells even in patients with sterile urine culture [2, 7].

Substances released by inflammatory cells could act as promotors of carcinogenesis or sensitize the epithelium for carcinogens [26]. In different in vitro and in vivo animal studies, increased levels of epidermal growth factor, transforming growth factor and cytokines, and increased expression of cyclooxygenase (COX)-2, were found in chronic inflammatory tissue and at the uro-intestinal anastomosis following ureterosigmoidostomy [9, 19]. A promising theory for proliferative anastomotic instability in urinary diversions could be local prostaglandin formation at urointestinal borderlines [7, 8]. Since increased levels of prostaglandins and other eicosanoids have been found in different proliferative tissues, including colon cancer, their key enzymes (COX-1 and COX-2) are under further investigation [9, 19]. Eicosanoids seem to have an important role in the multistep carcinogenesis (initiation, promotion and progression) of different human cancers, including colon cancer [7, 9, 18].

Late detection of a secondary malignant tumour leads to a poor prognosis due to metastasis to the peritoneum, lymph nodes and liver, causing lymph and blood to drain away. Most groups recommend sonography and excretory urography as well as annual endoscopy follow-up, the start of which is still controversial [2, 28].

The German Urological Association guidelines for follow-up after urinary diversion or bladder augmentation recommend annual endoscopic evaluations [2, 17]; however the majority of authors think that annual endoscopic follow-up beginning with postoperative year 3 for all forms of urinary diversion is a good compromise and should be recommended [2, 18, 26]. In cases of new-onset hydronephrosis, haematuria, or suspicious findings on excretory urography, sonography, computerized tomography or magnetic resonance imaging, immediate endoscopic investigations are mandatory [2].

40.5
Conclusion

The incidence of bladder tumours in patients with neurogenic bladder seems to be higher compared with that of the general population. Indwelling catheters, bladder augmentation, stones and chronic UTI are important risk factors for bladder cancer [2, 28]; however, bladder cancers are frequently muscle-invasive tumours and have a poor prognosis [29].

Immunological/pathological mechanisms and a prolonged exposure to carcinogens may be involved in bladder cancer carcinogenesis in patients with neurologic bladder [7, 9].

In general, all reported cases of bladder malignancy occurred after a lag time of at least 10 years [10, 18]. Furthermore, research should focus on the mentioned immunological/pathological mechanisms in patients with neurogenic bladder, as additional knowledge may help prevent recurrent UTIs and may aid in decreasing bladder tumour risk in these patients [23].

Finally, careful examination of microhaematuria, the prevention of recurrent UTI, and the avoidance of indwelling catheters are essential to minimize bladder cancer risk in these patients [5, 23].

For this reason all the authors strongly recommend endoscopic surveillance of all patients with a history of bladder augmentation beginning 10 years after initial surgery [27].

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Renal Failure and Neurogenic Bladder

41

Raphael Moog · François Becmeur

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41.1
Introduction

Whatever its origin, a neurogenic bladder dysfunction can result in renal damage and urinary incontinence. The results of the rates of renal failure in patients with neural tube defects show that they have actually eight times the risk of renal failure, and for people with paraplegia/quadriplegia the increased risk is five times compared with the general population [16].

Nerve damage causes impairments of the bladder and urethra. Detrusor hyperreflexia with or without detrusor–sphincter dyssynergia undermines safe effective and controlled storage and voiding urine. Persistently high intravesical pressure is the predominant factor responsible of renal damage. Intravesical pressure greater than 35 cmH_2O involves vesicorenal reflux, dilatation of the excretory system and renal damage. Urinary tract infections and nephrolithiasis are added factors.

The objective of treatment is, on the one hand, to preserve renal function in neonates and infants, and on the other hand, to achieve urinary continence in older children [3].

Most of the neurological lesions evolve with the growth, bladder, and renal status having to be regularly reevaluated.

41.2
Evaluation of Renal Function

Clinical symptoms that have to be explored are trouble linked with retention and incontinence. Overflow incontinence can be found at examination. Abdominal palpation can reveal an overflow voiding. In case of fever, urinary tract infection must be suspected; however, prevention requires systematic examination instead of awaiting clinical symptoms.

The initial examination should include a biological examination: glomerular filtration rate is considered to be the best marker of renal function [30]. Serum creatinine is a poor marker of renal impairment in paraplegic patients because of the varying degree of muscle atrophy. It is not sensitive enough in identifying early deterioration of renal function. The Cockroft-Gault formula was developed to calculate creatinine clearance from gender, age, body size, and serum creatinine. Although it is accepted as valid in a healthy ambulatory person, the calculated clearance is abnormally high in patients with muscle atrophy. This results from low creatinin production and reduced serum creatinine levels in the denominator. The use of lean body mass in the formula has not been proven accurate [18–21]. Inulin clearance is ideal to evaluate glomerular filtration rate, but it is expensive and clinically impracticable [11–18].

Cr-51 EDTA and Tc-99 TPA have been introduced to measure glomerular filtration rate. Glomerular filtration is calculated from the rate of tracer activity clearance from plasma after intravenous administration. The fact that is time-consuming and costly make this examination impractical for routine use.

Serum cystatin C has been advocated as a measure of glomerular filtration rate. Serum cystatin C concentrations have been shown to be closely related to the clearance of inulin, ^{51}Cr EDTA and ^{99}T DTPA. Values of reference of cystatin C are similar for both men and women. They‘re not correlated with the age for children older than one year, neither with the height nor with the muscle mass. [4, 12, 30].

Urodynamic testing is necessary to establish the type of bladder dysfunction.

Magnetic resonance imaging is the exam of choice for the aetiological research when an occult neurogenic lesion is suspected.

41.3
Prevention of Renal Deterioration

41.3.1
Mode of Bladder Drainage

Intermittent catheterization is the greatest progress in neurological bladder management. The 7-year decrease in the renal failure rate is the result of clean intermittent catheterization and of a better follow-up with treatment of urinary tract infections [19]. Crédé maneuver consists in abdominal expression in order to facilitate bladder emptying. In the past this maneuver was used extensively, but it can generate high pressure in the bladder notably when the sphincter is not denervated [26]. Clean intermittent catheterization can usually be performed in both boys and girls from neonatal period, if necessary. Follow-up confirms its efficacy in preventing renal deterioration. If it cannot be performed because of familial, social, or anatomic reasons, a urinary diversion is needed [3].

41.3.2
Paraclinic Follow-up

Urodynamic testing to define the type of neurogenic dysfunction enables planning of management strategy. Lack of voluntary control to contract the bladder and to relax the external urethral sphincter associated with detrusor–sphincter dyssynergia are the key reasons of micturian problems. Urodynamic evaluation permits determination of the capacity of the bladder, resting and voiding bladder pressures, to recognize detrusor–bladder neck and detrusor–sphincter dyssynergia, and to evaluate drug therapy and surgical acts [23].

In case of impaired storage capacity of the bladder with high voiding pressure exceeding 40 cmH_2O, different treatments can be implemented, including the following:

1. Anticholinergic drugs, such as oxybutinin chloride ,can be started with 0.2 mg/kg day^{-1} with gradually increasing dose. Adverse effects, such dry mouth, heat intolerance, mood change, and constipation, are dose dependent but reduce patient compliance. The response to treatment is monitored by clinical observation and urodynamic study [3].
2. Intravesical injection of botulinum toxin. Injections of botulinum-A toxin into the detrusor induced a significant decrease in the frequency of daily incontinence episodes, a significant increase in first uninhibited detrusor contraction, in maximum bladder capacity, and a significant decrease in maximum pressure of uninhibited detrusor contractions [17]. Botulinum toxin is a selective blocker of acetylcholine release from nerve ending. Technique consists of depiction of 30–40 submucosal injections throughout trigone, base, and lateral walls of bladder (Fig. 1). According to weight 100–300 U of botulinum toxin are injected [28]. The average duration of the toxin effect is 12 months at first and slightly longer at subsequent injections [2]. Resiniferatoxin can also be used but with fewer good results as botulinum toxin [6–7].
3. Bladder augmentation can be considered if there is a small contracted bladder with no sufficient response to the precedent treatment. Bladder neck closure and continent urinary stoma are indicated in patients with a damaged urethra or incompetence of the urethral sphincter. Detubularized ileal segment is generally used for bladder augmentation; gastric or sigmoid tissue can also be used. Routine annual evaluation with abdominal ultrasonography to assess for development of calculi should be standard. Cystoscopy in order to detect cancer has to be performed in cases of hematuria. With careful follow-up bladder augmentation can provide long-term clinical and urodynamic improvement for patients [24]. Urethral resistance can also favor high bladder pressure. It can be useful in some cases to reduce the urethral sphincter pressure.
4. Alpha-blockers are used to relax muscle tone [29].
5. Botulinum-A toxin injections in the external urethral sphincter through a cystoscope at doses of 50–100 U are effective in decreasing urethral sphincter resistance [14]. Straining, micturition time, dribbling, maximum flow rate, voiding pressure, postvoid residual, and urethral pressure improve after injections [2].

Transurethral section can be used if the previous technique failed.

Voiding cystourethrography must be part of the check-up. It is the best examination to search a vesicorenal reflux, which is one of the principal factors of renal damage (Fig. 2). Endoscopic treatment is indicated cases of reflux. Cystourethrography is less informative in the analysis of the proximal urethra than urodynamic study.

Urine cultures are necessary to authenticate urinary tract infections. Instead of systematic control, it is preferable to perform this examination when the patients present clinical symptoms such as fever, abdominal pain, or epididymo-orchitis. In asymptomatic patients using antibiotics may not be warranted.

Ultrasonography is the routine examination. It is used to determine excretory cavity status and vesical status. Ultrasound allows detection of renal and bladder stones which are common in these patients. Risk factors

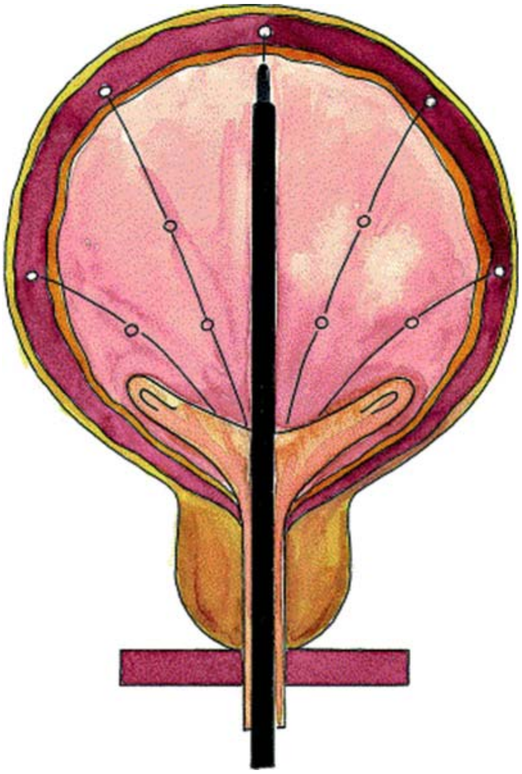

Fig. 1. Mapping of the injection sites of botulinum toxin. (From [17])

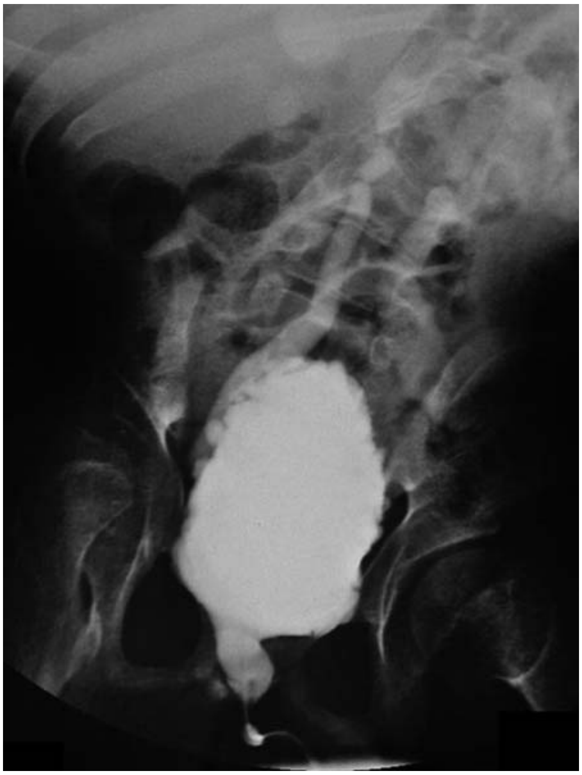

Fig. 2. Voiding cystourethrography of a patient with meningomyelocele: neurogenic bladder and vesicorenal reflux

for stone formation are urinary tract infection, urinary tract reconstruction or diversion, vesicoureteral reflux, pelvicalicectasis, and renal scarring. Standard therapies for stone disease have limited efficacy and recurrence is frequently observed [25].

Radioisotopic renography DMSA permits evaluation of relative function of each kidney. Many authors describe 30–50% of abnormal examination in patients with meningomyelocele [22].

41.4
Treatment of Renal Chronic Insufficiency

Acute renal failure must be feared; causative factors are urinary tract infection, obstruction in the urinary tract, hypotension, salt and water depletion, and drugs [9].

Whereas acute renal failure was a frequent cause of death before 1970, this is no longer the case. Mortality in adults with neural tube defects is primarily from respiratory disease, circulatory disorders, and neoplasm. Mortality is double that of the general population [16].

The kidney plays the major role of guardian of the internal milieu through excretory, metabolic, and endocrine functions. The kidney filters fluid and solutes and selectively reabsorbs and secretes water, electrolytes, and minerals. The kidney also regulates the amino acid pool, acid–base equilibrium, and hormone metabolism and excretion. The kidney hydroxylates vitamin D to its active form, which is the direct feedback inhibitor of parathyroid hormone. Erythropoietin is produced in the kidney to maintain normal erythrocyte mass. In chronic renal failure these functions may begin to fail when clearance is in the range of 50–75% of normal, and this can begin to alter growth rate and normal development of the child. In order to save residual renal function, nutritional measures are necessary, but this should not prevent a good physical development.

The best way to prevent early growth failure in children with renal disease is by the use of specified nutrition, and appropriate buffer, activated vitamin D, and calcium-containing phosphate binders as needed.

Supplemental sodium and water in children with polyuria and intravascular volume depletion may prevent growth failure. Children with acquired glomerular disease may need sodium restriction and, if treated with steroids, a diet low in saturated fat.

Hyperkalemia generally responds to salt and water repletion, but when glomerular filtration rates fall less than 10%, potassium-restricted diet is required.

Calcium supplementation and hydroxylated vitamin D can prevent renal osteodystrophy. Activated vitamin-D therapy should be started if PTH is elevated more than two to three times normal. If calcium phosphorus product is >70 mg/dl, calcium phosphate crystals can precipitate into tissues, decreasing serum calcium. Phosphate intake can be limited by using calcium barbonate or calcium acetate.

Anemia is an almost invariable feature of chronic renal failure. The major reason is an inadequate production of erythropoietin by the failing kidney. Recombinant erythropoietin is a part of the treatment of chronic renal failure, which needs constant iron supplementation to keep up with erythrocyte production.

Cow milk is detrimental in this group of individuals because of high solute and protein load, often causing intravascular volume depletion, hyperphosphatemia, and acidosis. Cow milk has to be replaced by a specified renal formula. Protein intake should be supplemented only in order to replace ongoing losses.

Hyperlipidemia should be monitored, and a diet restricting saturated fat may be sufficient with maintaining linoleic acid. Lipid-lowering medications are routinely not recommended. Angiotensin-converting-enzyme inhibitors can decrease urinary protein loss and may ameliorate hyperlipidemia.

Growth hormone stimulates height growth and increases muscle mass, and is indicated in children who have a significant growth delay or for whom standard conservative management has failed.

If the recommended daily allowance is not reached, feeding by a gastrostomy may be necessary.

Elevated blood pressure represents a risk factor for the deterioration of renal function and for cardiovascular death. Angiotensin-converting-enzyme inhibitor is indicated to lower the blood pressure with a specific role of halting the progression of chronic renal failure; however, caution must be exercised in advanced renal failure because of risk of hyperkalemia and an acute decrease of renal function [22].

All physicians caring for children with renal disease should have pediatric nephrology consultation available [27].

41.4.1
Dialysis

Once terminal renal failure has occurred, the mode of renal replacement should be made. Peritoneal dialysis is the therapy of choice in pediatric population. The advantage is a home therapy, however, with the necessity of an indwelling catheter with risk of peritonitis. The risk is potentiated in patients with ventriculoperitoneal shunt or urinary stomata. Having a ventriculoperitoneal shunt is not an absolute contraindication to peritoneal dialysis. If cerebrospinal fluid diversion is needed simultaneously or after starting peritoneal dialysis, an extraperitoneal site should be a better choice. Loss of peritoneal function is a potential late risk related to cerebrospinal fluid and peritoneal dialysis [8].

Hemodialysis is another mode of treatment which needs frequent hospitalizations and vascular access which is not so easy to obtain in these patients.

41.4.2
Renal Transplantation

Renal transplantation is the preferred therapy for patients with terminal chronic renal failure. In patients with abnormal urinary tract, there is a risk that the transplanted kidney suffers like the native kidney had suffered; therefore, the general strategy is to correct inefficiencies of the lower urinary tract before transplantation. Churchill recommended that the urinary tract have three essential features before transplantation: an adequate urinary reservoir with a safe low pressure; a competent urethral control mechanism to ensure continence; and a patent passageway and reliably consistent method of achieving complete bladder evacuation by voiding or clean intermittent catheterization [1–22]. With this reserve, results, in terms of graft survival, are the same in patients with neurogenic bladder as in other patients [20].

The timing of the cystoplasty is contentious [5]. If the urodynamic study indicates that cystoplasty is necessary, it should be made 6–8 weeks before transplantation so that its healing is not influenced by immunosuppression. Problems of dry cystoplaty can be managed by daily irrigation; however, when abnormal bladder function is not recognized before transplantation, successful bladder augmentation can be performed subsequently [13]. When possible, kidney transplant ureters should be drained to the native bladder.

41.5
Complications

Urinary tract infections are frequently encountered. Like stone formation infections can be prevented by regular drainage and irrigation of augmented bladder. The majority of patients who require clean intermittent catheterization have bacilluria and could receive continuous antibiotic prophylaxis with the risk of developing multiresistant organisms. For the patients who void spontaneously antibiotics are given for symptomatic urinary infections [5].

Perforation of augmented bladder can follow renal transplantation. Long-term steroid use and immunosuppression favor this potentially fatal complication.

Metabolic alterations are induced by contact between urine and absorptive bowel mucosa; however, there are other causes possible such as renal insufficiency, tubular dysfunction secondary to cyclosporine, or long-term prophylactic trimethoprim–sulfamethoxazole therapy. Alkali therapy is needed to correct metabolic acidosis [10–13].

41.5.1
Malignancy

The risk of uro-intestinal malignancy is documented by the follow-up of ureterosigmoidostomy, which is an overall risk of malignancy 80–550 times greater than that in the general population. For enterocystoplasty the incidence of malignancy has been comparably small to date. Patients with renal transplantation and additive immunosuppression should undergo periodic endoscopic evaluation [13].

41.6
Conclusion

Renal transplantation can be successfully performed in children with end-stage renal disease due to severe lower urinary tract dysfunction. Before transplantation, a stable urinary reservoir and storage system are necessary. Close surveillance is imperative in children who have undergone transplantation into an abnormal native bladder.

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Sexuality in Young People with Neurogenic Bladder Dysfunction

42

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42.1
Introduction

The sexual and reproductive health needs of young people with chronic illness and disability, including neurogenic bladder, have historically received little attention. This is consistent with widespread societal assumptions that adults with special health care needs are not sexually active or suppress their sexual needs, that they do not need sex education and that they are not subject to sexual abuse. These assumptions need challenging, consistent with the knowledge that, regardless of the presence of disability or chronic illness, "essential elements of good sexual health are a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. This requires the protection and fulfilment of sexual rights for every individual, such as equitable relationships, respect for bodily integrity, sexual fulfilment, access to services, sexuality education and information, and freedom from attitudinal, cultural, societal influences influencing behaviours" [3].

Young people with chronic illness and disability face the same hurdles as their otherwise healthy peers; however, they have additional needs and face different challenges that relate to their underlying condition [4, 5, 16]. Sexual behaviour is socially learned, moulded and reinforced within the environments of family, friends, community and school; thus, the expectations of friends and family and health professionals, both spoken or unspoken, can influence the expectations that young people develop of themselves as sexual beings. Sexuality is experienced within a social context. As young people with special needs experience greater social isolation, they commonly have fewer opportunities than their healthy peers for exploring their sexuality. This can be compounded by restricted physical mobility and greater reliance on adults for care, which can further reduce social engagement, opportunities for friendship, and intimacy.

The sexual and reproductive health care needs of young people with neurogenic bladder dysfunction are particularly important to consider, as it is much more likely that, as a result of the same pathology, sexual function is also affected. There has, however, been surprisingly little study of the sexual and reproductive health knowledge and function of this group, let alone any articulation of their sexual and reproductive health concerns or sexual health care needs.

The few available studies have primarily involved young people with spina bifida and adults with spinal cord injury who identify sexuality as an important part of life [20]. In an Australian study of sexual and reproductive health of 14- to 23-year-olds with spina bifida [14], almost all of the 51 young people reported that they had been interested in someone romantically, with two-thirds having been on a date or having had a boyfriend or girlfriend. Almost all of the young people wanted a partner and hoped to get married, with three-quarters wanting children; however, two-thirds of these young people were worried in one way or other about being in an intimate relationship.

The focus of this chapter is to review what is known about sexual and reproductive health knowledge and function in young people with neurogenic bladder dysfunction, to highlight the importance of addressing sexual and reproductive health care in this group of young people, and to explore strategies for how best this information can be communicated to young people and their families.

42.2
Sexual and Reproductive Function

There are different definitions of sexual activity. While it commonly refers to heterosexual vaginal sexual intercourse, it has also been defined in relationship to other forms of sexual activity such as masturbation. School-based population studies of sexual activity in young people report similar rates of sexual activity (both intercourse and broader activity) between healthy young people and those with various chronic illnesses and disability, although it is noteworthy that the more severe the disability, the less likely the young person is to be sexually active [4, 5, 16].

In the 1970s Dorner [8] identified very low levels of sexual activity in young people with spina bifida [8], with only 1 in 63 teenagers reported to be sexually active. More recent research has shown increased interest in sexuality and greater levels of sexual activity [2, 6, 7, 14, 19]. Using the definition of sexual intercourse, rates of sexual activity vary from 13 to 35% of males with spina bifida [2, 6, 7, 14]. Using the broader definition of sexual activity, rates of up to 65% of males overall have been described [19]. In females, reported rates of sexual intercourse vary from 37 to 53% [2, 14, 19], with rates of up to 80% for sexual activity when it includes masturbation and other forms of stimulation [2]. In the one controlled study of young people with spina bifida, 28% of adolescents with spina bifida reported they had "had sex" compared with 60% of a matched control group [6].

A few studies investigating sexual function after spinal cord injury have included people who were injured when young. Ferreiro-Velasco et al. [9] found that women whose spinal cords were injured before the age of 18 years were less likely to be sexually active than those who were injured after the age of 18 years [9]. They do not comment on whether the women were sexually active prior to the spinal cord injury, but these data suggest that people who are younger and less likely to be sexually active prior to injury are less likely to be sexually active even many years after injury. This highlights the importance of childhood and adolescence as a time when much of the foundation for future healthy sexual relationships is laid down.

When asked specifically about physiological sexual function, studies report that between 56 and 88% of males with spina bifida experience penile erection and 53–85% ejaculation [2, 7, 14, 19]. These studies found that those with lower lesions (L5 or sacral) and without hydrocephalus were more likely to be able to experience erection and ejaculation [7, 19]. Decter et al. [7] noted that all men with an anocutaneous (sacral) reflex could have erections, whereas those without were less likely to.

The proportion of women with spina bifida who report being able to experience orgasm varies from 37 to 54% [14, 19]. Sawyer and Roberts [14] found that 81% reported some genital sensation, which was considerably more common than the 37% who had experienced orgasm. As with males, higher lesions were associated with reduced sexual function, whereas lower level lesions (S1 and below) were associated with fewer problems [19].

The notion of sexual satisfaction in people with neurogenic bladder dysfunction has been primarily assessed in adults with spinal cord injury. These studies show a link between urinary continence and sexual satisfaction, with an improvement in sexual satisfaction when continence is achieved [9, 13, 18, 21]. Specifically, Vroege et al. [20] found that less than 50% of adults with spina bifida were satisfied with their sex lives: one in three was not satisfied. They also found that urinary and bowel incontinence were seen as potential impediments to sexual satisfaction; for the majority this was not insurmountable if care was taken for toileting or catheterisation prior to any sexual intimacy.

For young people with spina bifida, Sawyer and Roberts [14] found that two-thirds had worries about being in an intimate relationship, most commonly due to incontinence and more general concerns about having a disability. Clearly, concerns about physical differences and the requirement for self-care, such as intermittent self-catheterisation, create anxiety for young people negotiating friendships and sexual relationships. Reassuringly, three-quarters of young people in this study who were sexually active reported no problems in sexual intercourse; the remainder reported back pain and urinary urgency.

42.3
Sexual and Reproductive Health Knowledge

In an interview study of 57 adult males with spina bifida, Decter et al. [7] reported that 72% could accurately describe the basic concepts of reproductive physiology (e.g. that a fetus develops after intercourse results in fertilisation of an ovum by a sperm). More specifically, knowledge of the effect of spina bifida on sexual function was assessed by Sawyer and Roberts [14], who reported that only 25% of young people with spina bifida and 40% of their parents thought they knew how spina bifida affected their sexual function, with the remainder reporting that their knowledge of sexual health and spina bifida was either poor or extremely poor. Poor knowledge was confirmed following assessment of young people's and their parent's core knowledge about spina bifida and sexual health (see Table 1), with only one in four young people and one in three parents answering more than half of the factual questions correctly. Females and parents of females had better knowledge. It was interesting that during the interview, over half the young people asked specific questions about a wide range of concerns including reproductive capacity, fertility, childbearing and the risk of having a child with a disability. Questions such as "Can I pass on spina bifida to my partners by having sex with them?" and "Can I catch sexually transmitted diseases even though I have spina bifida?" show serious gaps in the sexual and reproductive health knowledge of this group of young people.

42.4
Why Health Care Providers Should Address Sexual and Reproductive Health in Young People

There are a large number of reasons why it is important for health care providers to address sexual and reproductive health concerns in young people with neurogenic bladder; these are summarised in Table 2 and outlined in detail below.

Young people with spina bifida have poor knowledge of the specific sexual and reproductive health complications of spina bifida, and they and their parents want more information [14]. This is important given the prevalence of sexual activity, however defined, especially in the context of low contraception use and high rates of unplanned pregnancy in women with spina bifida. Cromer et al. [6] found that only 16% of young people with spina bifida used contraception compared with 60% of the control group. Sawyer and Roberts [14] reported a much higher rate of contraception use, with 85% of sexually active young people reporting using contraception and 61% reporting very regular use; however, within the ten sexually active young women, three had had unplanned pregnancies which raises questions about the reliability of their contraceptive use.

An important, yet poorly reported, aspect of contraceptive needs of people with neurogenic bladder dysfunction is the possibility of latex allergy, which is important to consider when counselling about condoms, which are commonly made of latex rubber. Latex allergy has traditionally been highly prevalent in people with conditions such as spina bifida, or congenital abnormalities which have required recurrent surgery or interventions such as self-catheterisation, although rates are falling with the current practice of avoidance of latex contact from birth for risk groups [17]. High-risk young people should be advised to avoid latex condoms and instead use the variety of deproteinized latex or latex free condoms on the market [11].

No study of sexual and reproductive health in young people with spina bifida or spinal cord injury has assessed whether these young people are being screened for sexually transmitted infections (STI). Yet, young people with special health care needs are more likely to report ever having had an STI [16]. There are similarly no studies of other aspects of routine sexual health screening, such as cervical (PAP) screening, which raises concerns about how often such screening occurs in adult practice.

Almost all young people with spina bifida interviewed by Sawyer and Roberts [14] wanted to have children. There are, however, few reports of reproductive outcomes in people with spina bifida. Bomalaski et al. [2] report that only one man of 17 had successfully fathered a child. Decter et al. [7] report that 19% of men in their sample of 57 had attempted to father a child, with 8 of the 11 being successful. Sawyer and Roberts [14] report the concerning finding that 3 of 10 sexually active young women had had unplanned pregnancies. One of these pregnancies ended in a spontaneous miscarriage at 12 weeks, another in the term delivery of a child with a chromosomal abnormality after a pregnancy complicated by preeclampsia, and the third was ongoing at the time of the study. Bomalaski et al. [2] reported that 27% adult women with spina bifida had had a pregnancy, although no further details were reported.

An important aspect of reproduction in women with spina bifida (and who are partners of men with spina bifida) is periconception folic acid. Adequate intake of folic acid 1 month prior to conception and for the first 3 months of pregnancy (400 μm/day) prevents 70% of cases of spina bifida in the general population [12]. Given the low numbers of women with spina bifida who have children, the recurrence of spina bifida in this group is unknown. Family history is known to be an important risk factor, however, with women who have a child with a neural tube defect having a 30-fold increased risk of having a further affected pregnancy [12]. It therefore suggests that women with spina bifida (or who are partners of men with spina bifida) should be counselled about the importance of periconceptional use of folic acid. It is interesting that Sawyer and Roberts [14] found that only a quarter of young people knew that folic acid may reduce the risk of having a baby with spina bifida, and that of the three women in the study who had been pregnant (all unplanned), none had taken folic acid.

Table 1. Core knowledge about sexual and reproductive health and spina bifida. (From [14])

- Puberty often occurs earlier than usual in people with spina bifida
- Men with spina bifida usually have reduced fertility, but can still father children
- Females with spina bifida have normal fertility and can become pregnant
- The risk of having a baby with spina bifida if one partner has spina bifida is 1 in 25
- Both amniocentesis and ultrasound are useful in prenatal diagnosis of spina bifida
- There is an association between spina bifida and latex allergy (condoms)

Table 2. What health care providers should address in sexual and reproductive health

- Young people's concept of themselves as sexual beings is affected by neurogenic bladder dysfunction and associated co-morbidities
- Young people (and their parents) have poor sexual and reproductive health knowledge and want more information about sexual and reproductive health
- The underlying cause of neurogenic bladder dysfunction commonly and variably affects sexual and reproductive health
- Many young people with neurogenic bladder dysfunction are sexually active
- Many young people with neurogenic bladder risk unplanned pregnancy because of inadequate contraception use
- Young people with neurogenic bladder benefit from knowing about their likely future reproductive capacity and risk of passing on their condition to their children
- Young people with special care needs have higher rates of sexual abuse

Population studies have identified that young people with special health care needs have higher rates of sexual abuse than otherwise healthy peers. This is particularly true for people with a cognitive deficit [4, 16]. Specifically, investigating young people with spina bifida, Sawyer and Roberts [14] found that nearly one in three of 27 young women with spina bifida had received unwanted sexual attention of some type. This included unwanted touching or having something done to them sexually in 8 of these 10 young women. One of 24 males had experienced unwanted sexual touching. The mean age of onset of abuse in this group was 14 years, but ranged from 4 to 20 years. This high incidence of sexual abuse has important ramifications for care providers, parents and educators alike in terms of the range of prevention strategies that could be considered.

42.5

Sources of Information About Sexual and Reproductive Health

For young people with chronic illness or disability, the focus of health care is usually on the management of the day-to-day aspects of their condition, with less attention to broader developmental issues such as sexual and reproductive health. When seeing several medical and surgical specialists or multidisciplinary speciality teams, young people may not have regular contact with a primary health care provider, who more commonly provide sexual and reproductive health care than specialists. A challenge for all specialists caring for young people with special health care needs is to identify whose role it is to provide sexual and reproductive health care to the young person and to ensure that this role is performed.

Are young people sufficiently informed and what do they want to know? Decter et al [7] found that over half the males in their sample had learned some aspects of sexual and reproductive knowledge from the classroom, with 18% learning from parents and 14% from peers. Sawyer and Roberts [14] found that the majority of young people felt that they had received sufficient general sex education, primarily at school. Specific spina bifida sex education was a major deficit, however, with only 8% saying they had received sufficient spina bifida specific sex education. Eighty-four percent of patients reported receiving no spina bifida-specific sexual and reproductive health information. Perhaps not surprisingly, three quarters of young people in this study rated their knowledge of sexual health and spina bifida as "poor" or "extremely poor". When asked if they had ever discussed sexuality issues with their doctor, only one in three young people and parents reported that they had. Of note, only 5 of the 13 sexually active young people in this group had received some reproductive counselling. In two cases this was only after an unplanned pregnancy. Discussions had most commonly focussed on fertility, heredity, pregnancy and the oral contraceptive pill. Of the group who had not had discussions with a doctor, the overwhelming majority of young people would have welcomed discussions as long as they were initiated by the doctor. In this study two-thirds of young people identified their medical specialist (rather than the primary care doctor) as the person they would prefer to speak to about these issues; however, the importance of these issues is highlighted by the fact that one in five stated they would be happy to discuss these issues with *anyone*.

In adults with acquired spinal cord injury, three-quarters considered the information they had received from their doctors about the changes the spinal cord injury would cause to their sexual function was either insufficient or non-existent [9].

The role of parents in sex education for young people with spina bifida is not well studied. As with parents of healthy children, parents of children with special health care needs play a primary role in promoting the notion that sexuality is an integral element of what it is to be human. Sawyer and Roberts [14] found that parents were more likely to assume "asexuality" among their children than was the case. Parents were less likely to think their son or daughter with spina bifida had had a romantic relationship than young people reported and were less likely to think their son or daughter would get married and have children than what was expected by young people themselves. The question of who is right is less relevant than the question of how parents and health professionals can promote the expectation that in the future, children and young people will enjoy sexual intimacy (safely), despite illness or disability.

Promoting the expectation of future sexual intimacy can be particularly challenging in some circumstances, such as when young people with spina bifida have associated cognitive limitations. Concern about greater vulnerability to sexual advances can lead to parental over-protection. While this may be considered appropriate given the high rates of sexual abuse in young people with cognitive impairment [4, 16], overprotection can be expressed many different ways. Denying young people expectations of sexual futures is one form of over-protection, as is limiting opportunities for social engagement and sexual experimentation. While understandable anxiety about vulnerability – of their daughters in particular – may inform these behaviours, parents may unwittingly end up encouraging sexual "acting out" behaviours (such as multiple sexual partners, refusal to use contraception) by young people in order to unconsciously challenge such assumptions. Parents may require support in helping foster appropriate independence and resilience in their son or daughter.

42.6
Discussing Sexual and Reproductive Health with Young People and Their Families

Having established the importance of addressing sexual and reproductive health issues with young people with neurogenic bladder dysfunction and their families, consideration needs to be given as to how this is best achieved. There is no set time or format for discussing sexual and reproductive health issues with young people and their families. Individual concerns and sexual and reproductive health care needs change as young people mature through adolescence. It is important that information be provided to parents in order that that they be able to provide timely information and support for their child. An example is the notion of privacy around self-care which becomes more important as young people progress through adolescence. While this concept should be discussed in general terms with the family before adolescence, it may need to be more explicitly addressed in adolescence in relationship to specific activities or behaviours, such as intermittent self-catheterisation.

Young people progress through adolescence at different rates (see Table 3), although broadly, common themes are evident at different ages. For example, early adolescence (typically 10–14 years) is dominated by the physiological changes of puberty and is a time that is characterised by comparison with peers. Young people with special health care needs can be particularly vulnerable at this time, especially when their maturing cognitive capacity means they may develop insight about various implications of their physical disabilities. On the other hand, reduced cognitive function, even if subtle, can greatly affect young people's capacity for learning as well as their capacity to form meaningful social relationships at this time (and later in life).

Physical pubertal development is an important component of adolescent development. There is no evidence that menstruation is affected in neurogenic bladder dysfunction per se, although the aetiology of the condition must obviously be considered. Anderson et al. [1] found no effect of acquired spinal cord injury on the mean age of menarche and no increase in menstrual difficulties. In contrast, the onset of puberty and menarche is commonly earlier in young women with spina bifida, especially those with shunts. For example, Sawyer and Roberts [14] reported that the mean age of menarche in young women with a shunt was 10.3 years in comparison with those without a shunt in which it was 12 years (the mean age of menarche in Australia is 12.8 years). Reassuringly, within these 27 young women with a wide range of disability, only one 14-year-old patient required practical assistance with menstrual management.

Young people tell us they want health professionals to take the lead in discussing sexual and reproductive health. There should be little anxiety about raising these issues "before the young person is ready", as they will simply not pay attention to the information if this is the case; however, just raising the issue signals to both the young person and their family that sexual and reproductive health will be part of future discussions and hopefully gives them permission to subsequently ask questions about these themes.

Young people are likely to be embarrassed discussing aspects of sexual and reproductive health, at least at the start of any discussion. Health professionals are also commonly embarrassed [15], especially if they are uncertain of what to say. It may reassure health professionals to remember that young people (and their parents) are poorly informed and universally want to know more about sexual and reproductive health. While it is important that parents also be informed, young people commonly benefit from some time alone with the health professional to discuss personal information. It is important that health professionals be familiar with local confidentiality laws and practice, and explain these to young people prior to any discussion. Young people are much more likely to question and share important information with clinicians when it is known that these discussions are confidential. Discussions about the need for confidentiality and privacy also need to include parents so that they understand why the young person is seen alone.

Table 3. Adolescent development

Stages of adolescence	
Early	Coming to terms with body/biological changes
Middle	Establishing self among peers as a worthwhile individual
Late	Vocational/educational issues and one-to-one intimate relationships
Cognitive development	
Early	Concrete thought; lack future orientation/forward thinking Offer straightforward explanations and clear consequences
Middle	Developing abstract and complex thought; able to think more creatively, try out ideas; experimentation, risk-taking The challenge for clinicians is to ensure explanations to young people are meaningful, and to develop shared perspectives
Late	Greater levels of abstract thought; weigh-up multiple information; able to think hypothetically and plan ahead Usually remains "patchy" and more difficult to use new abilities in challenging situations

Table 4. The HEADSS approach. (From [10]

Headss	Area	Question
H	Home	Where do you live? Who do you live with?
E	Education	Are you at school? What year are you in? What are your grades like?
A	Activities	What do you do for fun? What do you do with your friends?
D	Drugs	Many people your age experiment with cigarettes, alcohol and drugs. What are your experiences?
S	Sexuality	Many young people become interested in sex at your age. Have you ever had a close friendship? What about a sexual relationship?
S	Suicide and depression	Many people feel sad and down at times. Have you ever felt like this? Have you ever thought life is not worth living?

Several assessment tools can assist clinicians take a psychosocial history. One commonly used approach is the acronym HEADSS, which is a useful screening tool [10]. Taking a clinical history using the HEADSS approach (see Table 4) is a strategy to engage young people within the health consultation, as well as informing one's broader understanding of a young person's social and educational context, while exploring their risk and resilience profiles in relation to mental health, substance use and sexual behaviours.

Using the HEADSS approach, one can shift focus from less sensitive to more sensitive topics, and to move from the third person (e.g. "Some young people your age are starting to be interested in forming sexual relationships. Is this the case with any of your friends?") to more personal discussion ("Have you ever had a sexual relationship?"). Care should be taken to use open-ended questions, language that is understood (appropriate for cognitive ability and culture) and to offer non-threatening explanations to young people's questions that will encourage them to share other concerns.

Important points for successful communication with young people are to be relaxed, non-judgemental, open and accepting. It is important to demonstrate respect and to implicitly and explicitly acknowledge potential issues such as culture, religion, gender and sexual preference within these discussions. It is also important not to assume prior knowledge of a young person's behaviours unless you have directly asked. An example of this is sexual orientation. Although heterosexuality is the norm, it should not be assumed, as the frequency of homosexuality is similar in those with or without special health care needs [4, 16].

42.7
Conclusion

Families and health professionals have important roles in creating expectations that young people with neurogenic bladder are sexual beings, just like other young people. Most young people with neurogenic bladder dysfunction hope they will have intimate sexual relationships and family life in the future, with many being more sexually experienced in adolescence than their parents realise. While some will have normal sexual function, others will have various difficulties with erection and ejaculation, orgasm, and reproduction. As a group, the evidence suggests that these young people have very poor knowledge of the specific difficulties they may experience in relationship to sexual and reproductive health, and that they and their families want more information. This group of young people have unacceptably high rates of unplanned pregnancy and sexual abuse, and it is unknown what routine sexual health screening they receive. Addressing sexual and reproductive health issues in a sensitive and age-appropriate manner is an important component of health in this group of young people.

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Metabolic Consequences and Long-Term Complications of Enterocystoplasty in Children

43

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43.1
Pathophysiology of Metabolic Complications

Bladder urothelium is designed to contain urine and the metabolic components that have been secreted by the kidney within the bladder. Here it can be stored for several hours without any of its component parts leaking back into the circulation. Bowel epithelium has been designed to absorb the contents of the intestinal tract, in a selective manner, back into the body fluid compartments, and therefore significant disturbances of a metabolic nature are to be expected [18, 25, 37].

Cells are joined together by a number of different mechanisms. Just as bricks in a wall need to be held together – and there are different methods of doing so – the cells need to be held together, too [10, 21]. Tight junctions occur in between cells close to the lumen and occur when the cell membranes fuse together [7, 17]. This provides the watertight seal between the epithelium/endothelium and the lumen of an organ.

Anchoring junctions occur between cells and also bind cells to the extracellular matrix; these are adhesive glycoproteins, such as fibronectin, and cell adhesion molecules which are calcium dependent, called integrins [5, 8, 33].

The other form of communication and linkage between cells are communicating junctions; these are like doors that could be opened and closed by an appropriate stimulus to exchange information between cells [1, 24, 36].

Because of the essentially different nature of urothelium and bowel endothelium, changes induced by reabsorption of the chemical components of the urine can be anticipated [34, 39]. When small or large intestine is used in lower urinary tract construction, one of the common metabolic conditions that ensues is hypokalaemic metabolic acidosis [2, 23, 31]. In this situation, ammonium ions and chloride ions are reabsorbed into the blood stream where in the liver, ammonium irons are metabolised to urea, which in consequence increases the acidic load on the body by freeing protons (H+) [4, 29, 30]. This leads to a degree of metabolic acidosis, and the hydrogen ions are buffered with bicarbonate and the resultant carbon dioxide is excreted by the lungs in an attempt to compensate for the metabolic acidosis, giving a respiratory alkalosis but leading to depletion of bicarbonate [27, 28]. The greater propensity of the large intestine to secrete bicarbonate is thought to account for the higher rate of this particular metabolic complication when segments of large intestine are used for urinary diversion. The bowel also reabsorbs water and the patient is therefore in a continuous cycle of water reabsorption and excretion, and with the consequent nephrogenic stimulus to maintain serum sodium levels and reabsorb sodium there is an inevitable loss of potassium in the urine [3, 22, 38]. Ileum tends to reabsorb potassium. whereas colon does not; therefore, hypokalaemia tends to be more problematic when colonic segments are used [9].

Whereas this is a theoretical and measurable complication of ileal and colonic incorporation in the lower urinary tract, it seldom causes much in the way of symptoms in children [26]. Tiredness, weight loss and polydipsia are the symptoms of hypokalaemic metabolic acidosis, and the treatment involves oral sodium bicarbonate and potassium citrate [32]. It is never extreme enough in augmentation surgery to require chloride transport blockers such as nicotinic acid or chlorpromazine, which are sometimes used in adult practice where large segments of intestine are in contact with urine [6, 13].

It is seldom the case that gastric epithelium is used for bladder augmentation, because of the high incidence of hypokalaemic metabolic alkalosis [14, 20]. While the acidosis that occurs after small or large bowel cystoplasty is relatively inconsequential in clinical terms, the metabolic alkalosis that occurs after gastrocystoplasty is a real and practical risk, occasionally causing catastrophic metabolic consequences [11, 19, 31]. The loss of hydrochloric acid into the urinary tract not only gives rise to a dysuric syndrome and haemorrhage from the bladder epithelium, but there is loss of hydrogen ions and chloride in large amounts as well [15, 36].

This may give rise to an acute metabolic illness where there are intractable seizures. The likelihood of this acute and life-threatening situation developing is apparently greater in patients who have a degree of renal insufficiency, and emergency treatment with intravenous normal saline with additional added potassium is required to correct the metabolic abnormalities [12, 27]. Death has been reported in this situation [16, 35]. Where there is a chronic low-grade hypokalaemic metabolic alkalosis, H2 blockers can be helpful in the management.

43.2
Vitamin Deficiency

As the terminal ileum is the most often used part of the bowel in cystoplasty, it should not be surprising that vitamin-B12 deficiency is sometimes a long-term metabolic consequence [23]. Provided 15 cm of terminal ileum are left, the incidence of this complication remains fairly low at approximately 2%, but where large segments of terminal ileum are used, because of technical considerations during the cystoplasty, long-term monitoring for megaloblastic anaemia and the neurological consequences should be mandatory [14]. It is thought to be more common in continent urinary diversion, because the relatively larger segments of terminal ileum are used in the diversion and long-term rates approaching 20% have been recorded [12, 31]. Treatment is relatively simple and consists of vitamin B12 monthly injections of 100 µg.

43.3
Bile Acid and Lipid Malabsorption

Removal of more than 100 cm of ileum for reconstruction is extremely rare in childhood practice, but if there is a deficiency of ileum due to previous resection or to short gut as in patients with cloacal extrophy, then removal of a small amount of ileum may tip the patient into fat malabsorption [31, 37]. The turnover of bile salts during the 24-h period is matched by hepatic bile acid synthesis and a balance between reabsorption of bile acids by the distal ileum and loss in the feces [15]. Loss of the ileo-caecal valve for any reason tends to increase bile acid loss, and a risk of fat malabsorption due to bile acid deficiency is not simply theoretical. The other consequences are that fat-soluble vitamins, such as A and D, are not absorbed adequately, and this leads to other effects, particularly bone growth and blood clotting [1, 7]. If the patient becomes symptomatic, a low-fat diet and oral cholestyramine are helpful. Loss of large amounts of liquid feces, due to loss of the ileo-caecal valve, can be helped with medication, such as Lomotil, to reduce intestinal activity [5, 28]. In adult practice hypertriglyceridaemia have been found where large amounts of ileum have been used to make ileal-orthotopic neo-bladders. What long-term effects this might have are as yet unknown [16].

Whereas many of these absorbative and reabsorbative problems are thought to get better with time as the ileal-mucosa becomes adaptive, and there is a degree of mucosal atrophy and decreased villous height, there are long-term consequences for children, based on bone loss and growth retardation.

43.4
Bone Growth and Calcium Metabolism

Whereas this is in some sense theoretical, there have been findings indicating a delay in growth in children who have had enterocystoplasty, and this may be due to bone demineralisation via hypokalaemic acidosis [18]. Recent work has suggested that patients in whom colon was used to perform the cystoplasty have a higher degree of long-term metabolic derangement and a higher incidence of metabolic acidosis [9, 30]. They also found changes in the growth pattern of children in whom sigmoid cystoplasty had been performed.

One of the confounding factors in trying to measure the linear growth in children with cystoplasty is that the majority of the patients have suffered spinal dysraphism, in which there are abnormalities in growth and development and motility, which also affect bone mineralisation. The cause of demineralisation is the chronic metabolic acidosis which leads to a slow release of calcium from bone in an attempt to buffer excessive hydrogen irons. This calcium ion is then excreted by the kidney and leads to chronic bone demineralisation.

Correction of the acidosis does not always lead to improvement, and some patients may require 1 alpha-hydroxy-cholecalciferol supplements orally [3, 21, 34].

43.5
Magnesium and Drug Metabolism

Other metabolic abnormalities, such as magnesium deficiency, which result in weakness and slurring of speech, have been recorded in patients with ileal incorporation into the urinary tract, and some drugs can be excreted by the kidney and re-absorbed from the gastrointestinal segment [8]. Methrotrexate toxicity has been reported in patients with ileal conduit, and those who have a continent diversion receiving chemotherapy should have constant urinary drainage if receiving drugs of this nature [5, 27].

43.6
Malignancy Risk

The risk of malignancy is thought to be due to a metabolic consequence when fecal bacteria, which are almost universally present in the neo-bladders constructed above, act on urinary nitrites to make nitrosamine compounds, which are known to have carcinogenic effects [4, 32].

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Latex Allergy in Children with Spina Bifida

44

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44.1
Introduction

Latex allergy has received worldwide attention during the past decade [2, 13]. Several factors make latex allergy unique. Latex products were in use for over a century prior to the diagnosis of latex allergy in epidemic proportions [1]. Unlike many IgE-mediated allergies, which are induced by a single or few major allergens, there are hundreds of proteins in latex products, with 11 allergens having been identified, each bearing numerous epitopes [23, 52].

Two distinct populations are particularly affected by latex allergy: health care workers (HCW) and children with spina bifida (SB) or other conditions requiring multiple surgeries early in life. Interestingly, these two populations appear to have sero-reactivity to different individual latex protein profiles [37, 39, 52].

The severity of allergic reactions to latex proteins is another distinguishing factor, as anaphylaxis has been unusually common among latex-allergic individuals [63, 80].

Although information is available regarding latex products and the levels of exposure required to elicit clinical symptoms in allergic individuals, less is understood about the amount of protein and time required or the relevance of the route of exposure during the development of sensitization [52, 83].

In this chapter we give an overview on this problem, with particular focus on patients with SB.

44.2
Historical Overview

The first widespread use of latex products in the medical field was in the production of dentures [2]. One of the first cases of urticaria to latex was a reaction to a dental plate, reported in 1927 [2, 12]. With the invention of the vulcanization process, the use of latex became widespread, resulting in its use to manufacture over 40,000 products at present [22, 52]. Halstead first introduced the use of latex surgical gloves in 1896 and the first reported case of contact urticaria to latex household gloves was described in 1979 [23, 38]. A year later, Forstrom reported contact urticaria caused by surgical gloves [51]. It was not until 1986 that the reactions to latex products were defined as being IgE-mediated and that the allergens were latex proteins contaminating the products [52, 54].

Between 1989 and 1992, there were over 1100 cases of allergic responses to latex products, with 15 deaths resulting from latex protein-induced anaphylaxis reported to the U.S. Food and Drug Administration (FDA) [65, 82]. An additional 1200 allergic reactions and 13 deaths had been reported by 1997 [23]. Over 9.9 million people are employed by the health care industry in the U.S., and of these, 2.9--12.1% are estimated to be latex-allergic [38, 52]. Additionally, approximately 1% of the general population may be sensitized to latex. Although the reasons underlying the increase in latex allergy are unknown, it has been suggested that several factors are involved [12]. Subsequent to the issuance of "Universal Precautions" in 1987, there was a tremendous increase in glove use in the U.S. Use increased from fewer than 1 billion pairs per year in 1987 to over 20 billion pairs of gloves in 1996 [22, 52]. This increase in demand for gloves resulted in changes in latex harvesting and manufacturing practices that may have altered the protein content and allergenicity of the gloves. Adverse responses to latex products fall into three major categories: irritant contact dermatitis (ICD); allergic contact dermatitis (ACD); and IgE-mediated responses, with an inverse relationship between prevalence and severity [52, 65]. Most responses are irritant dermatitis that do not require prior exposure and do not involve immunological memory. Most irritant responses have been attributed to friction between the glove and occluded skin and to the donning powder, which is often alkaline. Numerous chemicals are added to latex during manufacturing and many are irritants and/or sensitizers [23, 52]. The second most frequent adverse reaction is allergic contact dermatitis, a T-cell-mediated hypersensitivity response [38]. Many chemicals used as accelerators and vulcanizing agents in the manufacturing process are contact sensitizers. Although irritant and allergic contact dermatitis are not life-threatening, they cause significant morbidity and reduced work performance. Irritant and allergic contact dermatitis disrupts the skin barrier and alters the normal physiology of the skin, which may lead to development of the more serious, but less frequent, IgE-mediated responses to latex proteins [52].

44.3
Epidemiology

The incidence of sensitization to natural rubber latex (NRL) is still unknown but estimated to be less than 1--2% in the general population [4, 8]. Anyone who routinely wears NRL gloves or is regularly exposed to NRL in an occupational setting may be at risk of developing latex allergy. The risk of sensitization tends to decrease with age. [11, 14, 88].

The epidemiology of NRL allergy, particularly in health care workers, as well as the general population, has been the subject of some controversy [24, 27]. Perhaps this is because identification of NRL allergy on a population-wide basis is not straightforward. In the clinical setting, NRL allergy is usually diagnosed based on a compatible clinical history and documentation of IgE sensitization [28]; thus, in a population study, documentation of IgE sensitization without clinical symptoms is not equivalent to identifying clinical NRL allergy [6, 50, 88].

Another major problem is that tests intended for clinical use may not perform optimally when applied to screening low-prevalence populations for a condition such as IgE sensitization to NRL [56, 61]. Clinical tests are optimized for use in evaluating patient populations where there is usually a high pre-test probability for the condition of interest [26, 52]. Assuming constant sensitivity and specificity, the higher the true prevalence of a condition, the more accurately a test will identify the prevalence of that condition in a population [70, 76]. If a condition is present at low prevalence, a larger proportion of test positives will be false positives, resulting in poor positive predictive value of the test and overestimation of prevalence. In the case of tests for IgE sensitization to NRL, the three in vitro tests available for use in the U.S. have reported specificities of 97, 97, and 73%, respectively, relative to skin prick test (SPT) [26, 50, 52, 77]; thus, even if the true prevalence of IgE sensitization to NRL were zero, these tests would identify 3, 3, and 27%, respectively, of a population as being sensitized [52, 93]. Other studies suggest similar performance for serological assays. In contrast, other authors reviewed available studies using SPT to estimate the prevalence of NRL sensitization in general population groups and found that estimates from such studies were in the range of 1% [6, 52, 88].

44.3.1
Latex Allergy in the General Population

A number of studies have examined the prevalence of IgE sensitization to NRL (as opposed to clinical evidence of allergy) in the adult general population [8, 28]. A study screening sera from 1000 U.S. blood donors for anti-NRL IgE using the AlaSTAT assay reported a 6.4% prevalence of positive tests [14, 52, 88].

Another study using three separate laboratories to screen 1997 U.S. blood donors with the AlaSTAT assay reported prevalence rates of positive tests ranging between 5.4 and 7.6% [52, 88, 93]. A study of British blood donors using the AlaSTAT assay found prevalence rates for NRL sensitization of approximately 4% in the winter and 7% in the summer [52, 88].

Cross-reactivity was noted between NRL and grass allergen. These prevalence rates are not much different from the background false-positive rates that would be predicted from the reported specificity of the AlaSTAT assay relative to SPT [56].

Two European studies have evaluated the prevalence of NRL allergy in all children presented for evaluation in allergy clinics. In one study, 2.2% of 453 children had positive SPT to an NRL extract [52, 76, 88].

Half of the sensitized children reported symptoms related to NRL exposure, mostly triggered by contact with balloons and gloves. In another study, 3269 children undergoing allergy evaluations were screened for NRL allergy by SPT with 1.7% positive, 1.1% of whom confirmed by re-examination [52, 88]. One percent exhibited a combination of positive SPT, RAST, and glove challenge.

44.3.2

Latex Allergy in Children with Spina Bifida

Children with SB are clearly at increased risk for both NRL sensitization and anaphylactic reactions to NRL during surgery [93]. NRL sensitization rates ranging between 34 and 65% have been reported [52, 56]. In this population, direct internal and mucosal contact with NRL medical devices may be the route of sensitization, as factors such as number of operations, and use of NRL devices, such as catheters or ventriculoperitoneal shunts, have been associated with increased risk of NRL sensitization and allergy. Atopy has also been documented to be an important risk factor [52].

The risk of anaphylaxis in the operating room is 500-fold greater in patients with SB as compared with control groups [88].

44.3.3

Latex Allergy in Health Care Workers

Over the past decade, clinical NRL allergy has been an important occupationally related disease among health care workers [28]. Exposure of latex-sensitized health care workers to NRL can lead to a range of allergic symptoms including contact urticaria, rhinoconjunctivitis, asthma, or even anaphylaxis. Atopic health care workers have consistently been found at increased risk for both sensitization and clinical disease [24, 52]. Latex allergy can be considered an occupational hazard particularly in health-related professions. Overall, the rate of sensitization to latex in health care providers is around 10% (range 0--40%) [52]; however, clinically symptomatic latex allergy is estimated to affect 1--2% of health care providers [56, 61]. In addition to physicians and dentists, health care workers reported to have especially high risks include operating room personnel, dental assistants, laboratory personnel, hospital housekeeping personnel, and ambulance attendants [52]. Some epidemiological studies have questioned the occupational nature of type-I (immediate hypersensitivity) latex allergy [27]; however, conclusions based solely on the results of serological tests may be misleading. Health care providers wear latex gloves frequently and for an extended period, and there is evidence that with sufficient exposure, employment in the health care field can lead to an increased risk of IgE sensitization to NRL [52, 88].

Other non-health care occupations with regular exposure to latex gloves, such as housekeepers, cleaners, rubber-band, surgical-glove and latex-doll manufacturing workers, have comparable rates of sensitization [11, 52, 88].

The number of reports on non-occupational cases of latex allergy is increasing, probably reflecting significant exposure of general population to a variety of latex devices, cross-reacting fruits, or pollens [52, 88]. There are cases in which the reactions have occurred at home in individuals with no occupational exposure to NRL or history of frequent surgical procedures [61, 88].

44.3.4

Latex Allergy in Atopic Patients

Atopy, defined as evidence of an individual developing IgE antibodies to one or more common environmental allergens, is common among latex allergic patients, and is a risk factor for NRL sensitivity. Latex allergy has been reported to be fourfold more common in atopic subjects as compared with non-atopic controls [24, 88].

44.3.5

Latex Allergy Associated with a Pre-existing Hand Eczema

Pre-existing hand eczema is present in more than one-half of patients with NRL allergy and is often mentioned as a risk factor. Chronic hand eczema and atopy often coexist and such patients often wear NRL gloves that increase their exposure to NRL protein allergens [88, 93]. Chronic hand eczema, either atopic, irritant, or allergic in nature, may mask signs of contact urticaria to NRL, and latex allergy should be suspected in patients who develop pruritus, burning, and stinging upon exposure to natural rubber latex gloves or other natural rubber latex devices [77, 88]. Some glove-wearing NRL-allergic patients may have only persistent hand eczema, which may be the initial sign that a patient has become allergic to latex. Alternatively, repeated contact urticaria from latex gloves may evolve into chronic hand dermatitis [61, 88].

Concomitant hand eczema may be another manifestation of latex allergy. A number of patients with type-I immediate hypersensitivity to latex may have relevant positive patch test reactions to rubber chemicals or mixes, glutaraldehyde, latex gloves, and preservatives [11, 88]; thus, it is important to emphasize that concomitant type-IV (delayed-type hypersensitivity) and type-I (immediate hypersensitivity) allergies to rubber products may occur in the same patient. Chronic hand eczema may also occur without type-IV allergy to rubber chemicals and may resolve avoiding latex glove use. Irritant or allergic contact dermatitis may further facilitate type-I sensitization to latex by disrupting the epidermal barrier and allowing latex proteins to penetrate the skin [88, 93].

44.4
Reports of Latex Allergy and Its Sequelae

Most immediate hypersensitivity reactions to latex are severe, and occur within 10 min of exposure [29]. Usually, allergenic latex proteins come in direct contact with the skin and mucous membranes or are inhaled after binding to the corn-starch powder in rubber gloves, causing symptoms of a type-I (immediate hypersensitivity) allergy [2, 50]. Holzman et al. report a series of 162 patients with allergy with an age range of 1--31 years: the primary diagnoses were myelodysplasia in 139 patients, extrophy of the bladder in 10, and cloacal extrophy in 11 patients; 1 patient had undergone a tracheo-esophageal fistula repair in infancy requiring repeat dilatations with red rubber bougies, and 1 patient was allergic to latex for reasons not apparent in his medical or surgical history [30, 46, 50]. Anaphylaxis occurred in the operating room in 26% of these patients [49, 53]. In addition, 22% of the patients had allergic reactions at the dentist's office and 17% had allergic reactions to latex balloons [50]. Cremer et al. report that 5 (8.3%) of 60 latex-sensitised patients with SB had experienced intraoperative anaphylactic reactions. Anaphylactic reaction can be the first presentation of latex allergy without preceding milder allergic symptoms [50, 78, 87]. Those patients who present with anaphylactic reaction usually have high levels of latex antibodies, but the converse is not always true: in fact patients with high levels of latex antibodies can remain asymptomatic without any evidence of any allergic reaction to latex [46, 50]. Ownby et al. report anaphylaxis associated with latex allergy during barium enema examinations in six patients, with one death. Some studies have found a gender difference in latex allergy, with a female predominance in the adult population in some and a male predominance in some others. This variance, however, may simply reflect local referral patterns [50, 78]. It is possible that environmental control with the use of washed latex equipment and avoidance of chemoprophylaxis are appropriate and successful for children with latex allergy undergoing surgical procedures [2, 50, 53]. Nevertheless, these measures may not be adequate to prevent anaphylaxis in latex-allergic adults.

Children with SB are usually receiving prophylactic antibiotic and anticholinergic medication for urinary tract problems [46, 50]. Usually such patients have many additional allergies and sensitivities. Several patients have shown signs and symptoms of allergies with positive intradermal tests of sensitivity to morphine, fentanyl, lidocaine, pancuronium, and succinylcholine. Cross-reactivity of latex and tropical fruit allergies is not uncommon [50].

44.5
Diagnostic Tests for Latex Allergy

Direct IgE mediation appears to be the pathogenesis of the anaphylactic response to latex [50, 88]. Exposure to a foreign substance can lead to IgE-mediated anaphylaxis when a susceptible person comes in contact with an allergenic protein in its native state or as a hapten [17, 31]. This type-I (immediate hypersensitivity) reaction is also known as anaphylactic reaction [50, 88, 99]. Antigen binding to IgE antibodies initiates anaphylaxis [32]. Prior exposure to the antigen or to a substance of a similar structure is required to produce sensitization, although the patient may be unaware of any allergic history [33, 50, 88]. On re-exposure, binding of the antigen to specific IgE located on the surfaces of mast cells and basophils liberates histamine and chemotactic factors involved in anaphylaxis, and also other chemical mediators, such as leukotrenes and prostaglandins [43, 50, 88]. The mediators liberated produce a complex of bronchospasm and upper airway edema in the respiratory system, vasodilatation and increased capillary permeability in the cardiovascular system, and urticaria in the cutaneous system [34, 50, 66, 88].

Diagnosis of latex allergy may be based on a positive in vitro radioallergosorbent (RAST) and/or a positive in vivo skin prick test (SPT) and/or a positive provocation test result, each in conjunction with concordant clinical history [45, 50, 88]. Ideally, the design of diagnostic latex reagents for both in vivo and in vitro tests should be based on the representation of all allergenic proteins of NRL [50, 72, 88].

There are numerous reports in the literature about cross-reacting allergy. It is assumed that there are common epitopes in natural rubber latex and in some fruits [50, 79, 88].

44.5.1
The Importance of the Clinical History

The diagnosis of NRL allergy should be suspected in high-risk patients and in anyone with a history of urticaria or angioedema of the lips when inflating balloons; itching, burning, or contact urticaria when donning gloves; a history of adverse reactions to barium enema examinations or perioperatively; or urticaria or other immediate systemic symptoms (ocular, nasal, or pulmonary) from exposure to other latex devices [50, 88, 92].

44.5.2
In Vitro Tests

Latex-specific IgE antibodies in serum can be demonstrated in vitro and quantified with RAST or enzyme-linked immunosorbent assay (ELISA) [95]. The results of these tests are categorized into seven classes, where class 0 indicates absence and classes I--VI indicate presence of latex-specific IgE [98]. A positive in vitro test result may be diagnostic of latex allergy. Some authors only consider positive patients with a class-2 or greater RAST result [33, 34]. Serological assays may misclassify up to 25% of skin-prick test (+) latex-sensitized patients as serologically negative. Tests sensitivity varies between 50 and 90% and specificity as 80--87%. [45, 66]. The disadvantages of serological testing include the cost, delayed results, lower sensitivity, and accessibility as compared with in vivo testing; however, serology should be the initial diagnostic step in suspected latex allergy, because it is safer than in vivo tests [79].

44.5.3
In Vivo Tests

Skin-prick testing (SPT) is the gold standard in the diagnosis of latex allergy. Compared with in vitro serological assays, SPT offers the advantages of being substantially more sensitive, cheaper, easier to perform and providing immediate results [92]; however, the sensitivity of SPT is profoundly influenced by the quality of the latex extract used. Because the sensitivity of a single latex eluate is below 100%, it is important to use a panel of latex extracts to increase sensitivity [31]. Although SPT is usually safe, uncharacterized eluates made of NRL gloves may significantly vary in quality, stability, and allergenic concentrations, with the potential to provoke systemic reactions, including anaphylaxis [17]. Accordingly, SPT should be performed by an experienced staff and with available oxygen, epinephrine, and latex-free resuscitation equipment.

A standardized commercial SPT allergen preparation is available in Europe. An FDA-approved NRL skin test reagent is still unavailable in the U.S. [66, 72]; thus, extemporaneous extracts of Hevea brasiliensis or of high allergen gloves are often used for SPT. False-negative reactions may occur with low allergen glove extracts. Non-ammoniated latex seems to be the candidate SPT reagent of choice in FDA licensure because of its stability and practical quality control [66, 72].

In patients with food intolerance, SPT with specific foods can be performed. Because cornstarch may be used as a latex glove powder, SPT with cornstarch may rule out cornstarch allergy.

44.5.4
The Wear/Use Tests

The wear test (use test) is a validated glove provocation procedure and may be employed when there is a discrepancy between SPT or specific IgE results and clinical history. It is initiated as a one-finger test, and progresses to a whole hand test if there is no urticarial reaction after 15 min [79]. An extended test daily up to 1 week is recommended in doubtful cases. Non-latex vinyl gloves are used as controls. The current problem with the use of that test is that no standardized test material is available and latex gloves are now often less allergenic, rendering them unsuitable challenge materials [95].

44.5.5
Patch Test

In patients with hand eczema, patch testing may reveal allergens relevant to delayed-type hypersensitivity to rubber accelerators and antioxidants (mercaptobenzothiazole, black rubber mix and carbamates), glutaraldehyde, latex gloves, vinyl gloves, condoms and NRL [31]. When testing rubber accelerators, there may be discordance between petrolatum-based chemicals and the thin-layer rapid use epicutaneous (TRUE) test allergen system; therefore, positive reactions to rubber allergens may be missed if the TRUE test is used alone. Patch testing with NRL itself is not without risk and may rarely lead to serious immediate hypersensitivity reactions in patients with type-I latex allergy [33, 92].

44.5.6
Other Tests

In latex allergic patients with symptoms of upper airway obstruction and bronchial hyperresponsiveness, confirmation of diagnosis is usually accomplished by serial monitoring of pulmonary functions (pre-shift, mid-shift, and post-shift PEF or spirometry) at work [17, 88]. This workplace challenge is the gold standard for diagnosis of occupational latex-related asthma. Specific inhalation challenge with powdered gloves offers a definitive diagnostic method but should be offered in specialized challenge laboratories capable of dealing with acute severe reactions [88].

44.6
Risk Factors in Patients with Spina Bifida

Patients with SB are at high risk of latex sensitization (presence of cutaneous and/or serum latex specific IgE) [5, 10]. Some sensitized subjects may present clinical reactions to latex, whereas others have no symptoms after exposure to products containing latex proteins [97]. Several factors may be relevant to a high risk of latex symptoms in subjects with SB and latex sensitization [6, 16]. Some authors have shown that high levels of serum-specific IgE to latex, positive responses to latex SPT, a high number of operations, and a personal history of atopy were significantly associated with symptoms to latex in patients with SB and latex sensitization [26, 44].

An association between latex sensitivity and foods is well known and has been reported at the clinical level, in terms of skin sensitization (e.g., milk, egg white, wheat), degree of RAST, and/or immunoblotting inhibition [48, 50]. In vitro studies are important to confirm a cross-reaction between latex and food; however, specific IgEs for food allergens have never been studied because of possible risk factors for clinical reactions to latex in patients with SB and latex sensitization [6, 55, 57].

Some reports found a prevalence of latex sensitization equal to 25% in subjects affected with SB and about 30% of them with latex sensitization seem to show clinical reactions to latex [62, 91]. These subjects rarely present severe systemic clinical reactions to latex: the most frequent clinical reactions were urticaria and conjunctivitis. Symptoms arose shortly after patients had used latex gloves and inflated latex balloons [16]. Cremer and coworkers showed that primary latex prophylaxis during surgery can prevent latex sensitization in young SB patients. Some authors have found that the risk of latex sensitization in patients with SB exposed to latex was 38%, whereas this risk was reduced to 0 when latex exposure was avoided [55].

Several authors assessed the association between the presence of latex symptoms and the concentrations of specific IgE to latex and found that a value of RAST CAP for latex >3.5 kU/l was a significant risk factor for the onset of latex symptoms [57, 62, 88];\ therefore, in subjects with SB and latex sensitization, either a positive latex SPT (especially with a large skin weal) or a RAST CAP to latex >3.5 kU/L is a risk factor for the onset of latex symptoms [6].

Anyway some authors report that routine testing for latex allergy in patients with SB is not recommended [6, 26, 88].

It has been reported that any previous surgery episode increases the risk of latex sensitization 13-fold and that latex sensitivity increases with age in surgically treated children, with expected increments of 16% each year [6, 88]. The correlation between multiple invasive procedures and an increased risk of latex allergy has also been demonstrated for adults, where a history of more than ten operations was significantly correlated with latex allergy [6, 50, 88]. Direct mucosal and parenteral exposure to latex during medical procedures may be fatal in patients with latex allergy [5, 6, 88]. Latex hypersensitivity may be responsible for up to two-fifths of cases with intraoperative anaphylaxis. A recent survey in France rated latex allergy as the second most frequent cause of anaphylactic reactions during anesthesia [6, 88].

44.7
Clinical Manifestations and Their Management

Clinical symptoms of NRL allergy are dependent on individual susceptibility to the allergen, the mode and route of exposure and the type and amount of bioavailable protein allergen [7, 18].

Exposure to latex antigens can occur by cutaneous, respiratory, mucosal, and parenteral routes, with the latter two routes having the greatest risk for anaphylaxis [25, 35]. Symptoms usually result from direct contact with an NRL product but may also result from inhalation of aerosolized powder containing NRL proteins [36, 40].

The spectrum of clinical findings may range from contact urticaria to fatal anaphylaxis.

Localized pruritus/burning/stinging, contact urticaria, generalized urticaria, allergic rhinitis, allergic conjunctivitis, angioedema, bronchial asthma, and anaphylaxis may occur [41, 59].

44.7.1
Contact Urticaria, Respiratory, and Other Systemic Reactions

Contact urticaria presents as a spectrum of cutaneous manifestations (pruritus, burning, erythema, edema) usually starting within 15 min of exposure and disappearing without treatment within 1--2 h [60, 88]. As sensitivity and exposure to allergen increases, urticaria may eventually spread to the contiguous areas of the skin and disseminate [64, 88, 96]. Contact urticaria and angioedema may result from casual contact with donning powder residue on furniture surfaces or clothing, respiratory difficulties may be elicited by the snapping of powdered gloves in the proximity of sensitized patients, and anaphylaxis may occur by exposure to trace amounts of latex carried home on clothing or on food handled with powdered latex gloves. Mucosal swelling or anaphylaxis may occur after oral, vaginal, or rectal exposure to NRL products (balloons, gloves, condoms, dental, rectal, gynecological examinations) [69, 88].
Although cutaneous exposure to NRL most likely results in contact urticaria, extracutaneous symptoms, including allergic rhinitis, allergic conjunctivitis, facial edema, bronchial asthma, and even some cases of anaphylaxis, have been reported [74]. Anaphylaxis may occur outside the health care system from toy balloons, baby bottle nipples, pacifiers, squash balls, food handled with latex gloves, condoms, and even adhesive latex hair

bandages [88]. Pumphrey et al. emphasize the dangers of less obvious sources of latex allergen, which may lead to anaphylaxis [88, 89].

Even with prompt intervention, latex-induced anaphylaxis may be fatal.

Latex-related occupational bronchial asthma is estimated to affect 2.5% of exposed health care and manufacturing workers. The preponderance of latex-associated respiratory illness appears to be linked to the use of powdered latex gloves. Some affected individuals continue to experience asthmatic symptoms, even without contact with NRL devices [88, 94].

44.7.2
Latex-Fruit/Food Allergy Syndrome

Allergic reactions to multiple fruits and foods appear to occur with unusual frequency and severity in patients with latex allergy. At least half of latex allergic patients have fruit/food sensitivity and up to half of these patients experience severe reactions from foods [7, 88].

Reactions to various plant-derived foods from phylogenetically different sources, such as avocado, chestnut, banana, and kiwi (the four most frequently associated allergens), papaya, walnut, melon, peach, plum, celery, carrot, apple, pear, mango, apricots, grapes, passion fruit, pineapples, citrus fruits, fig, wheat, barley, hazelnut, potato, tomato, lettuce, and spinach, have all been documented [88]. Immunological cross-reactivity between NRL proteins and other conserved proteins and enzymes of the botanical world (such as patatin, profilin, papain, bromelain, chitinase, glucanase, and hevein) may at least partially be responsible for the unexpectedly high prevalence of food allergy in latex allergic patients [36, 88]. Milk allergy may also be associated and has been attributed to casein, which is sometimes added in the manufacture of latex. Latex-allergic patients may also have allergy to pollens (such as ragweed and grass), because of profilin, which cross-reacts with latex. Recently, homology between latex allergens and mold allergens has been termed the “latex-mold syndrome” [40, 88]. Even tobacco has been reported to contain prohevein-like defense-related protein, which may cross-react with latex [88, 94].

Some individuals with latex-food allergy may be uniquely sensitized to the antigens that are present in the food, simultaneously demonstrating clinical reactions to both the food and to the NRL products [18, 88]; therefore, a pre-existing fruit allergy may represent an additional risk factor for a clinically relevant latex allergy. Alternatively, some patients with latex allergy may have IgE antibodies to the fruits or plants without ever eating them; thus, it is not always clear whether latex sensitization precedes or follows the onset of food allergy [25, 88]. Patients with food allergy may present with a variety of manifestations including oral itching, generalized pruritus, hives, angioedema, laryngospasm, nausea, vomiting, pyrosis, and dyspnea after eating foods that cross-react with latex [88, 96]. Because the initial manifestation of food allergy may be anaphylaxis, patients should be educated about the risk of food allergy and be instructed to carry a personal epinephrine syringe [88].

44.7.3
Treatment

Allergic reactions from NRL exposure should be treated in a conventional fashion. The only current treatment specific to NRL is avoidance of the allergens. Persons afflicted with NRL allergy should not personally use or undergo procedures using NRL devices such as gloves or catheters. Non-NRL alternatives now exist and should be substituted [41, 52, 88]. Because aerosols generated by the use of powdered NRL gloves can affect bystanders, persons in the vicinity of the affected individual, such as co-workers, should switch from the use of powdered to non-powdered NRL gloves [52, 59, 88]. Latex-free operative theatres exist in some hospitals, and this is an adequate place where to operate patients with SB. If problems persist despite these measures, complete elimination of NRL from the affected individual’s surroundings must be considered. In the case of health care workers, institution of avoidance measures has allowed workers to continue in their occupations with decreased symptoms, and has been associated with falls in levels of serum anti-NRL IgE. A small study of specific allergen immunotherapy for NRL allergy was recently reported in which immunotherapy was associated with symptomatic improvement and decreased sensitivity to conjunctival challenge [35, 52, 88]; however, four of nine actively treated patients experienced a number of significant systemic reactions during therapy [52, 88]. Specific allergen immunotherapy remains an experimental treatment for NRL allergy, and will always be of lesser importance than NRL allergen avoidance [52, 60, 88]. Patients with NRL allergy should be counseled about their condition, especially for the risk of anaphylaxis if exposed to NRL during medical procedures, and should wear medical alert bracelets indicating their NRL allergy [52, 88, 94].

44.8
Recommendations for Prevention and Prophylaxis

Early identification of individuals with NRL allergy might allow early institution of avoidance measures, preventing progression to a more severe form of the disease [3, 52]. The natural history of latex allergy is not fully understood, and it seems that latex allergy may be related to frequent exposure to latex in the hospital environment, especially the operating room [19, 50]. All SB children should be protected from exposure and sensitization by avoiding the use of latex products whenever possible [20, 42]. Careful screening for a clinical history of latex sensitivity should be performed in all patients considered in the high-risk group (SB and urogenital-anomalies patients) [47, 50].

There is no scientific evidence to support the use of premedication with antihistamines or steroids to prevent IgE-mediated reactions when the antigen itself can be avoided; in practical terms, premedication has failed to prevent latex anaphylaxis in the postoperative period in patients with a positive history of latex allergy [50, 58, 67].

For patients with clinically apparent latex allergy rigorous avoidance of all contact with latex throughout the hospital stay is the first and most important method of management [68, 84].

A list of latex-free items can be made available in the hospital ward and operating rooms to facilitate the process of providing a latex-free environment for patients during their stay in hospital. With a latex-safe protocol in place, latex-allergic patients can be expected to experience an allergic reaction rate of 0--0.3% [3, 50, 85].
It is advisable to keep a cart of latex-free products, particularly gloves, at the beside of all such patients, and to put a sign on the door alerting visitors and hospital employees to the potential hazard of latex-containing products [50, 86].

Because of cross-reacting antibodies between latex and banana, it would be sensible to suggest that children who are known to be at risk of developing latex allergy, or who are already allergic to latex, omit bananas from their diet [26].

Considering that there is currently no cure for latex allergy, personal or environmental latex avoidance and substitution should be the most effective therapy for latex allergy; however, complete avoidance, particularly in medical settings, is practically impossible because of the abundance of NRL-containing products, and the realistic aim should be to minimize latex exposure [42, 88].
In general, as a primary prevention, all non-sensitized individuals in high-risk groups should use non-latex or low allergen NRL gloves and avoid other contact with NRL devices as much as possible [67, 88] Oil-based hand creams or lotions should not be used while using latex gloves, as this may cause glove deterioration [88]. After removing latex gloves, hands should be washed with a mild soap and dried thoroughly. Treatment of concomitant hand eczema is important to reduce the risk of latex sensitization [67].

As a secondary prevention, latex allergic patients should ideally wear only non-latex gloves, if there is little potential for contact with infectious material [88]. They should carry non-latex gloves at all times for health professionals to use during examinations and emergencies [86, 88]. Patients at risk should have a list of substitute latex-safe products for hospital and home duties, cross-reacting fruits and occult sources of NRL exposure [42].
Latex-allergic patients should obtain medic-alert identification bracelets and inform health care providers and their employers of their diagnoses [88].

As for environmental avoidance, in 1991 the U.S. Food and Drug Administration (US FDA)required all latex manufacturers to perform a two-step washing procedure [20, 88]. The first is during a step in the production process called leaching, and again after the product is finished. This aimed at removing many of the allergenic NRL proteins within latex products [58, 88].
In 1997, the US FDA required all medical latex devices to be labeled as such and to carry a caution that latex can cause allergic reactions [88].

These efforts have certainly improved the quality of medical latex devices, particularly medical gloves, within the market, and have decreased the clinically significant allergic reactions to latex [19, 88].

44.9
Conclusion

In the past decade, much information on latex allergy has been generated. We have gained an understanding of the clinical history, gained experience in recognizing symptoms, and identified major risk factors and groups [9, 15, 52]. By studying the allergens, routes of exposure, and exploring animal models, information necessary to prevent most potentially life-threatening reactions has been obtained [21, 52, 71]. Substitution of powdered latex gloves with low-protein powder-free or synthetic alternatives appears to be reducing the frequency of latex allergy in patients with SB [52, 73, 75].

For this reason, considering the risk factors for developing sensitization, it seems significant that babies have not been routinely exposed to such risk during delivery, from the use of latex gloves by midwives and obstetricians, over the past 30 years [26, 81]; however, considerable work still lies ahead. Information about the natural history of latex allergy and progression of the disease is still lacking. The diagnosis of latex allergy continues to be problematic in the U.S. and elsewhere, because no licensed skin-test reagent is available, and the approved serological tests have less than optimal performance characteristics [52, 86]. The development of standardized or recombinant latex reagents holds promise for increased testing accuracy and the potential for immunotherapy [9, 52, 90].

Continuing education can help latex-allergic patients avoid products causing reactions and provide a reasonable approach to managing their disease [52].

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Congenital Neuropathic Bladder Dysfunction: Diagnostics and Prevention of Complications

45

Guy A. Bogaert

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45.1
Introduction

Congenital neuropathic bladder dysfunction is the most common primary cause of urinary bladder and sphincter dysfunction and is frequently associated with secondary malfunction of the lower and upper urinary tract. Congenital and acquired abnormalities of the spinal cord are the primary cause of bladder dysfunction in children. Although the incidence of congenital neural tube defects appears to be decreasing, 95% of the affected children still present with neuropathic bladder dysfunction as a urological complication. Early detection and treatment is essential to prevent deterioration of the lower and upper urinary tract.

Treatment of congenital neuropathic bladder dysfunction should assure the following:

1. Normal development of renal function
2. Bladder and bowel continence
3. Self-confidence, independence and social integration, respect for normal sexual desire

To achieve these goals, early diagnosis and regular follow-up is necessary.

45.2
Embryology and Incidence

Congenital malformations of the spinal canal arise from an information defect of the neural tube. Already by the third week of gestation, the neural tube develops as a result of medial migration of the ectodermal neural folds. Interruption of this migration early in gestation can be either extensive of focal. If the interruption is extensive, the infant will develop either anencephaly or rachischisis, both situations being incompatible with life; however, if the interruption is only focal, spina bifida will result. By the end of the fourth week, the vertebral bodies in normal spinal cord development are formed from lateral mesodermal somites. If the neural tube fails to form, medial migration of the somites is blocked, thus interrupting the posterior fusion of the vertebral arches. This causes the malformation known as spinal dysraphism.

The exact cause of congenital spinal dysraphism is unknown; however, there are several teratogenic substances or situations, such as alcohol and zinc, maternal infection, and exposure to higher temperatures, caused by either fever or exposure of hot tubs and sauna, that may have an influence. A conclusive correlation of these teratogenic substances has never found, however [53, 54].

In addition, it is probable that environment and epidemiology may have an influence. There are studies that show a higher incidence of spinal dysraphism in the United Kingdom [25, 28]. Although there are no known genetic defects, there is a heredity factor: parents with one child with spina bifida have a 4% risk of having another affected child. In addition, parents with two children with spina bifida have an increased incidence of 12% to have another child with spina bifida.

The prevalence at birth of both anencephaly and spina bifida has decreased, but the advent of antenatal diagnosis and elective termination of affected pregnancies has undermined the reliability of birth prevalence rate as an estimate of incidence.

It is presently accepted that prophylactic intake of folic acid before conception decreases significantly the incidence of neural malformations, but again, a scientific explanation is unknown [81].

45.3
Screening

Screening for spinal and neural malformations has moved from screening of maternal presence of alfa-fetoproteins toward the ultrasound diagnostic [19]. The reason for this shift is the low specificity of an elevated maternal alfa-fetoprotein and fetal neural defects. Only in 7% of all pregnancies with repeated prenatal elevated maternal alfa-fetoproteine values does the newborn have a neural malformation [79]; however, a neural malformation is found in more than 70% of newborns if the first alfa-fetoprotein value before the 24th week of gestation was three times as elevated as normal [85].

Ultrasound not only focuses on the vertebral malformation and the spinal defect, but also detects associated problems such as polyhydramnion, malformation of the feet or legs, or asymmetry of the ventricles [2]; therefore, ultrasound alone detects a spinal defect in >63% of all cases [16].

The combination of ultrasound and alfa-fetoprotein values in the detection of spinal canal defects therefore has a sensitivity of >80% and a specificity of 99% [19]. An early and accurate detection means that the parents can be counseled. As mentioned previously, in practice a high number of elective pregnancy terminations will result in the lower incidence of neonates born with spinal dysraphism [12].

Another advantage of the early diagnosis is the possibility of delivery of children with spinal dysraphism in centers with expertise, and the possibility of immediate surgical care. It is still unknown if there would be any advantage or disadvantage between normal vaginal delivery or cesarean section [6, 32].

45.4
Prenatal Intervention

Prenatal intervention of open spina bifida or myelomeningocele is now performed in selected patients and presents an additional alternative to obstetricians and neonatologists counselling pregnant parents with a fetus and a spinal dysraphism. Initially, and this means prior to 1997, only fetuses with life-threatening anomalies and very poor predicted outcome were considered candidates for fetal surgery [52]; however, after gaining experience, it is now believed that the earlier in gestation the repair is performed, the better is the outcome. This statement is also based on the experience that damage to the spinal cord is progressive through gestation.

The recent experiences are now focusing on closure material that may obviate tethering and its long-term complications. It has been shown and proven that early fetal intervention reduces the hindbrain herniation associated with the Arnold-Chiari-II malformation in open spina bifida. In the United States, a multicenter (three centers) prospective randomized clinical trial of 200 patients began in 2003. It will take some time before one can clearly state if there is any benefit and if any of the complications are ever to be prevented [78].

Up to now it appears form the clinical observations and reports that fetuses with spina bifida treated in utero appear to have the same changes in urodynamic parameters and anatomical abnormalities in the urinary tract as other children with spinal defects who have undergone standard postnatal care; however, the long-term effects on bladder function in the fetus after in utero repair of myelomeningocele remain unknown [35].

45.5
Neonatal Urological Care

The immediate care of a newborn with spinal dysraphism must consist of a multidisciplinary team of neonatologists, specially trained pediatric nurses, social workers, pediatric urologists, and neurosurgeons.

From an ideal (pediatric urological) point of view, a urodynamic exam of the bladder should be performed before surgical closure of the spinal canal; however, mostly the urodynamic exam is performed after the neurosurgical closure. Due to this neurosurgical closure, a spinal shock bladder, an atonic detrusor muscle, is most frequently present and requires intermittent catheterization. To assure normal renal development, it is very important to maintain a low pressure in the bladder as urinary reservoir. So if in-between catheterizations the child is wet, it might be that there is a high intravesical pressure.

It must be emphasized that there is no contraindication or technical problem performing intermittent catheterization in newborn babies. It is better for the parents to become familiar with the intermitted characterization techniques as soon as possible [13]. It is recommended to use soft-tip catheters or prelubrified catheters and the size may be 8–10 Charrière/French to prevent

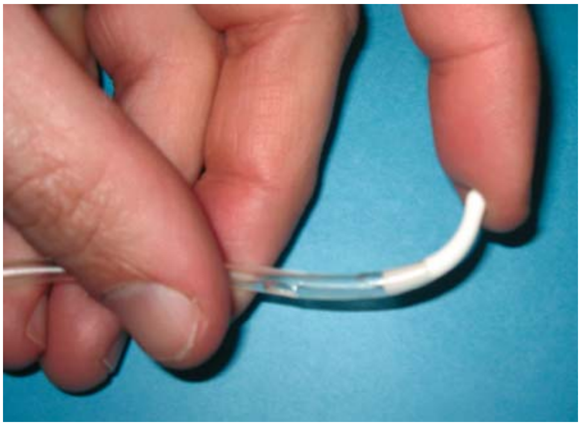


Fig. 1. Catheter with a soft atraumatic and flexible tip (Ergothan tip, Medical Service, Teleflex, Germany)

complications in chronic intermittent catheterization (Fig. 1) [72].

45.6
Occult Spinal Dysraphism and Spina Bifida Occulta

Occult spinal dysraphism is to distinguish from the spina bidifa occulta, which, according 10% of the normal population, is not correlated with pathological malformations of the neural canal. The diagnosis of closed spinal defects is not always evident. Frequently the diagnosis is made after obvious neurological, orthopedic, or urological complications [22].

Then initially unremarkable symptoms, like those of a hairy patch, naevus, or lipoma, can be considered as suggestive regional signs [44]. Urological complications, such as incontinence and recurrent urinary tract infection, are frequently the first symptoms in small children with spinal dysraphism. If the diagnosis is made early by ultrasound or magnetic resonance imaging, an adequate treatment can prevent severe complications.

It is important to differentiate occult spinal dysraphism from the well known “spina bifida occulta,” which is represented in 10% of the normal population and is not associated with pathological changes in the spinal canal. Urological complications and problems, such as urinary incontinence and recurrent urinary tract infections, may be the first signs and symptoms of occult dysraphism associated with neuropathic bladder function problems [46]. If this neuropathic problem is discovered and diagnosed early with ultrasound and magnetic resonance imaging, early treatment can influence the ultimate outcome positively [40].

45.7
Urological Diagnostic and Treatment of a Newborn with Congenital Spinal Dysraphism

To prevent urological (renal) complications the first goal should be to ensure or to create a low-pressure urinary reservoir. It might be that after the immediate neurosurgical closure, the detrusor becomes atonic and the intravesical pressure is low; however, this situation, also called spinal shock bladder, is temporary and unpredictable in time.

To evaluate the bladder pressure and function, the only tool is a urodynamic investigation or a videourodynamic investigation. McGuire et al. have studied the importance of determining the leak-point pressure during the urodynamic exam. This intravesical pressure reflects the value of maximal bladder capacity that is just higher then the pressure of the external sphincter. If these values are over 40 cm of H_2O, the children are at a higher risk to develop complications of the upper urinary tract [51]. On the other hand, but most probably in the same line, Bauer and Hallett have demonstrated that children with external sphincter dyssynergia have a significantly higher risk of developing complications of the upper urinary tract [5].

If at birth ultrasound shows hydronephrosis, it is mostly a symptom of renal damage secondary to a high intravesical pressure. An immediate treatment consisting of anticholinergic drugs [oxybutynine 0.1mg/kg q3 (oral or intravesical) or tolteridine 0.1 mg/kg q1] to lower the intravesical pressure and intermittent catheterization to ensure that low-pressure emptying is mandatory.

As mentioned previously, it is usually impossible to perform a urodynamic study before the newborn neuropathic closure, so that the immediate decision for urological treatment will depend on the ultrasound of the abdomen [5, 57, 61]. In general, about 27% of the children have a (low-pressure) spinal shock atonic bladder, whereas 73% have symptoms of (high-pressure) detrusor overactivity combined with an external sphincter dyssynergia [3].

In summary, it is the combination of the result of the first possible videourodynamic exam where the situation of reflux, shape, and volume of the bladder, and the status of the external sphincter, is observed, together with the results of the ultrasound exam, where the eventual renal damage is observed, that determines the first algorithm; however, it must be mentioned that this algorithm or management can change several times throughout the development of the child. A possible algorithm at birth is demonstrated in Fig. 2 [65].

The videourodynamic evaluation is performed as a combination of a classic voiding cystourethrogram with simultaneous pressure and electromyogram recording. Special attention must be given so that the filling rate re-

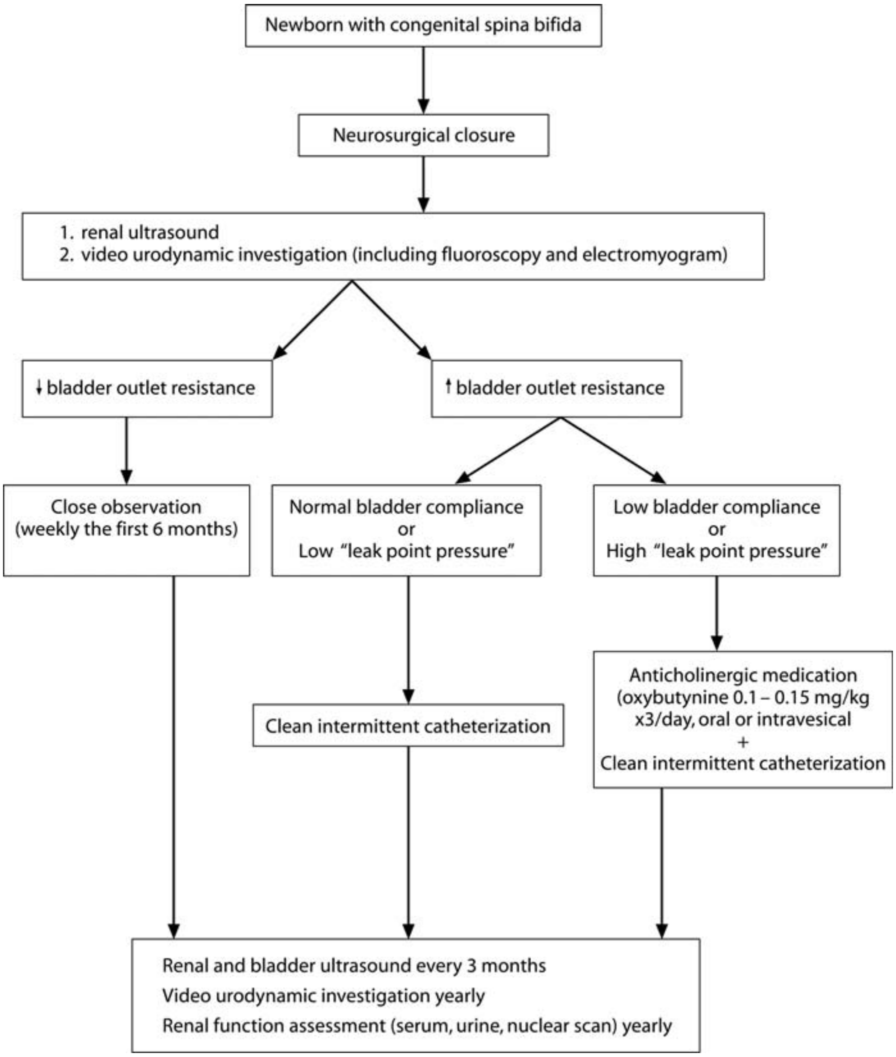

Newborn with congenital spina bifida
Neurosurgical closure
1. renal ultrasound
2. video urodynamic investigation (including fluoroscopy and electromyogram)
↓ bladder outlet resistance
↑ bladder outlet resistance
Close observation (weekly the first 6 months)
Normal bladder compliance or Low "leak point pressure"
Low bladder compliance or High "leak point pressure"
Clean intermittent catheterization
Anticholinergic medication (oxybutynine 0.1 – 0.15 mg/kg x3/day, oral or intravesical + Clean intermittent catheterization
Renal and bladder ultrasound every 3 months
Video urodynamic investigation yearly
Renal function assessment (serum, urine, nuclear scan) yearly

Fig. 2. A possible algorithm for treatment

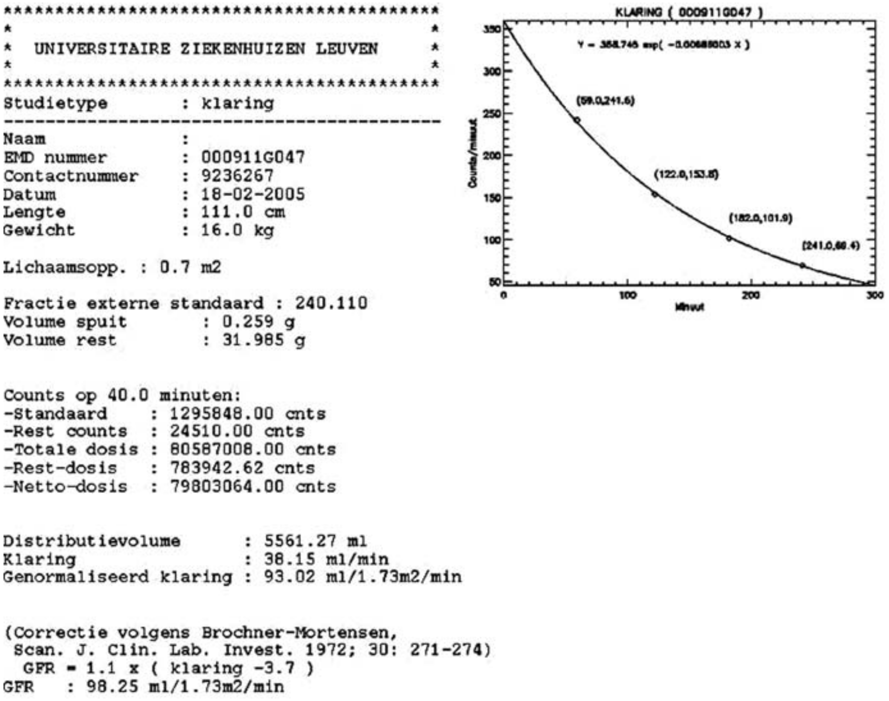
mains at a speed of 10 ml/min and the contrast medium at body temperature.

The video part of the videourodynamic evaluation is very important. It is also important to perform fluoroscopy at least every 10 ml, i.e., every minute during the filling, to evaluate and detect vesicoureteral reflux, as well as the status of the bladder neck and external sphincter, at several filling statuses and pressures.

The videourodynamic evaluation is the most important opportunity in early detection of the eventual impairment of the upper urinary tract, and it must be repeated at regular intervals to ensure appropriate and normal development of renal function [3].

To test renal function and have baseline renal evaluation, at the age of 3 months (or earlier, if necessary) a MAG-3 nuclear scan can determine the relative distribution of renal function between the kidneys, and gives an idea of eventual drainage from the kidneys to the bladder. Simultaneously with this exam, a Chroom-EDTA exam can be performed as this isotope reflects and determines the global glomerular filtration rate (see Fig.3).

Long-term urodynamic investigations and follow-up have shown that treatment with anticholinergic drugs to lower the intravesical pressure, and clean intermittent catheterization to avoid high pressure during bladder emptying, can successfully obviate renal function deterioration in the situation of detrusor overactivity [13, 24]. This treatment regimen was initiated and described by Lapides et al. in 1971 [42]. Since then, several studies, also form other authors, have repeatedly shown that intermittent catheterization is a simple and efficient method to be performed also in newborns [29]. Figure 3 demonstrates the picture from the urodynamic investigation at birth, whereas after 3 months of oral oxybutyine (3×0.1 mg/kg day^{-1}) the bladder volume became al-



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*  UNIVERSITAIRE ZIEKENHUIZEN LEUVEN     *
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Studietype        : klaring
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Naam              :
EMD nummer        : 000911G047
Contactnummer     : 9236267
Datum             : 18-02-2005
Lengte            : 111.0 cm
Gewicht           : 16.0 kg

Lichaamsopp. : 0.7 m2

Fractie externe standaard : 240.110
Volume spuit          : 0.259 g
Volume rest           : 31.985 g


Counts op 40.0 minuten:
-Standaard     : 1295848.00 cnts
-Rest counts   : 24510.00 cnts
-Totale dosis  : 80587008.00 cnts
-Rest-dosis    : 783942.62 cnts
-Netto-dosis   : 79803064.00 cnts


Distributievolume        : 5561.27 ml
Klaring                  : 38.15 ml/min
Genormaliseerd klaring   : 93.02 ml/1.73m2/min


(Correctie volgens Brochner-Mortensen,
 Scan. J. Clin. Lab. Invest. 1972; 30: 271-274)
  GFR = 1.1 x ( klaring -3.7 )
GFR    : 98.25 ml/1.73m2/min
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Fig. 3 Cr-51 EDTA radio-isotope clearance rate, measured by four blood samples, to determine the glomerular filtration rate. The value is normalized and corrected for body surface (extrapolated to 1.7 m^2).

most normal (55 ml) and the right-sided vesicouretereal reflux disappeared.

In contrast to this approach, Teichmann et al. have proposed close observation with ultrasound, urinanalysis, and early interventions [76]; however, the long-term results regarding clicnical complications, development of renal function, and quality of life have never been reported.

What is known and reported is the good acceptance of clean intermittent catheterization if it is introduced as early as possible in life, so that it will become a part of the daily routine [3, 5, 50, 73].

45.8
Long-Term Urological Treatment

What is true for the immediate treatment remains valid for the long-term treatment of congenital neuropathic bladder dysfunction due to spinal dysraphism: creating a low-pressure bladder reservoir to assure continuous drainage of urine associated with a low-pressure emptying process (renal development). A second goal is to make these children continent; in other words, an adequate urinary sphincter tonus or bladder outlet resistance will assure urinary continence. Possible complications that may influence the long-term treatment are vesicoureteral reflux, recurrent urinary tract infections, bowel dysfunction, tethered cord syndrome, early onset of puberty, sexual dysfunction, and problems with socialization.

To avoid long-term complications from frequent intermittent catheterization catheterizations in the male urethra, the size and quality of the catheter is very important. Ideally, catheter with a soft atraumatic and flexible tip (Fig. 1) or prelubrified catheter are advised. With the flexible tip it is already possible to safely use 8- to 10-Charriére/French in newborns. In pubers or adolescent, the size of the catheter should increase up to 16–18 Charriére/French.

The bladder capacity in children with neuropathic bladder dysfunction should be minimal, with the calculated normal value for their age to ensure storage of an appropriate urine production during 3–4 h: (Koff rule: (age in years + 2) × 28 in milliliters) [39].

Medical treatment with an anticholinergic drug, such as oxybutinine 0.1–0.15 mg/kg three times a day (orally or intravesically) or tolderodine 0.1 mg/kg per day, will increase bladder capacity with simultaneously lowering of the intravesical pressure. Possible side effects are dry mouth or further worsening of the constipation. Alternatively, the intravesical application of oxybutynin can be used to avoid systemic complications [47]. There is no contraindication for chronic treatment of anticholinergic drugs.

In some children, the anticholinergic treatment cannot provide an increase of bladder capacity, of which surgical measurements must be taken. In the neonatal period, and in case of insufficient effect of anticholinergic drugs and simultaneous upper urinary tract problems, a vesicostomy can a sure appropriate drainage of the urine [70]. The technique of a Blocksom vesicosto-

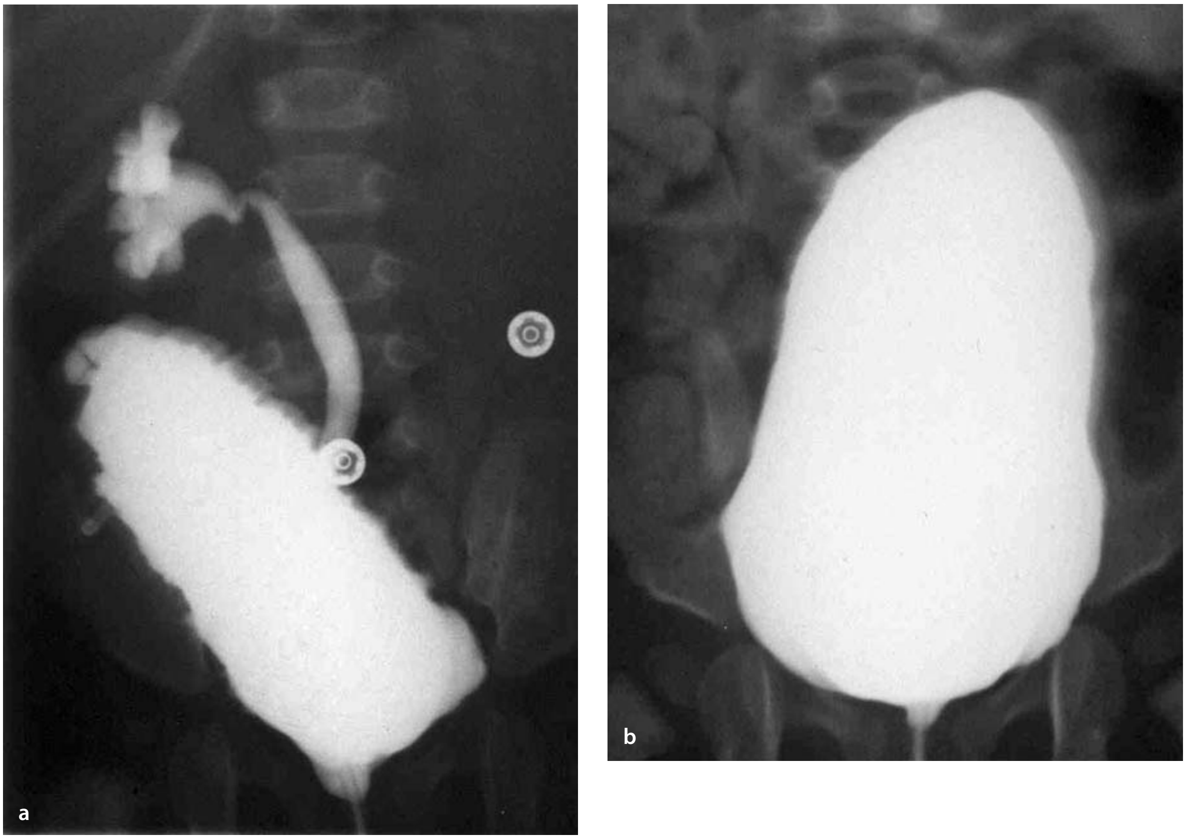


Fig. 4. Videourodynamic investigation before (**a**) and after (**b**) oral oxybutynine 0.10 mg/kg X 3/day to lower the bladder pressure. The vesicoureteral reflux disappeared within 3 months of treatment.

my is advised; however, one should always keep in mind that surgical measurements resulting in incontinence may well assure renal development and function but create significant problems such as skin problems or social integration of the child; therefore, it is important to perform reversible surgical procedures.

If the videourodynamic investigation shows a low-compliant bladder, a non-compliant bladder, or if the bladder does not respond well to the anticholinergic treatment, the bladder should be augmented. Figure 5 demonstrates the tracing of a low-compliant and therefore "unsafe" bladder together with the simultaneous videorecording. There is no vesicoureteral reflux and the child starts to leak a pressure over 30 cm H_2O and a volume of 145 ml (leak-point pressure >30 cmH_2O).

A surgical bladder augmentation can be achieved by incision of the detrusor muscle, detrusor myotomy, or by interposition of a good compliant tissue, an augmentation cystoplasty. In the situation of detrusor myotomy, the detrusor muscle is incised and the mucosa is allowed to build a large bladder diverticulum [17]; however, the long-term results of this technique are not favorable. Another possibility to augment the bladder without using non-urological tissue is the augmentation with a dilated ureter [82]. But also in this situation the long-term results vary and are not consistently positive.

The most common surgical approach to augment a small neuropathic bladder is the augmentation with intestinal segments. Stomach, as well as small and/or large bowel, can be used. The most common segment of the intestinal tract is the small bowel [23]. Alternatively, a piece of large bowel or a combination of small and large bowel is also commonly used [14, 64]. After augmentation with small or large bowel, the children are at risk of developing a chronic acidosis, which is more prominent in situations of a pre-existing renal insufficiency. In children with renal insufficiency, an augmentation with a piece of the body of the stomach could create an additional acid secretion through the bladder [9]. In addition, acid secretion will create a very low pH in the urine and the stomach produces less mucus, which prevents bacterial growth [8]. Gastrocystoplasty in children with neuropathic bladder problems after 10 years have demonstrated good results; however, much longer results have not been published [9]. Gastrocystoplasty has lost popularity because it can cause, on one hand, hematuria dysuria symptoms, and on the other hand, dangerous hypochloremic alkalosis.

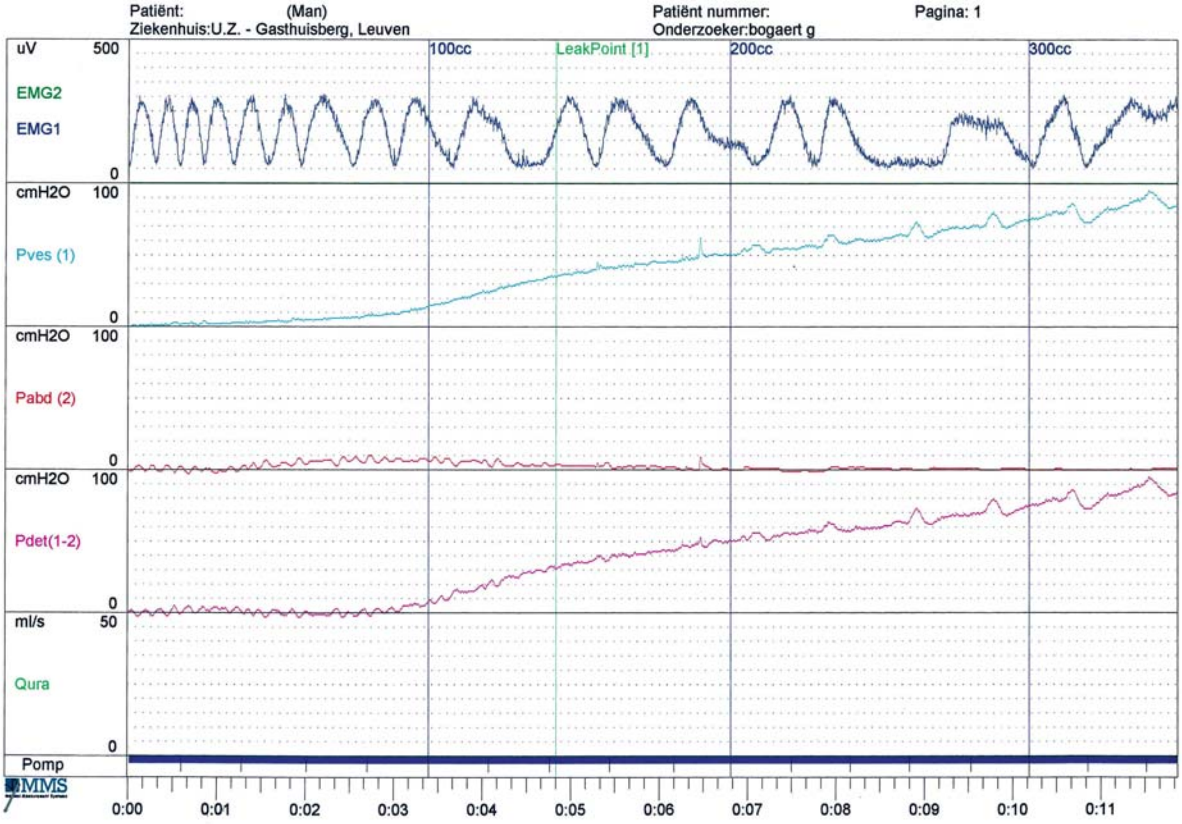


Fig. 5. Tracing of a low-compliant "unsafe" bladder together with the simultaneous videorecording. The child started to leak at a pressure over 30 cmH_2O and a volume of 145 ml (leak-point pressure >30 cmH_2O)

45.9
Urinary Incontinence

If the external sphincter mechanism is insufficient, it may be a safe, low-pressure situation initially, but later, when continence is required, it may become complicated and difficult to solve. The child may be partially or total urinary incontinent as the result of an insufficient bladder outlet. As a non-surgical solution, it might be attempted to increase the bladder outlet with alpha-adrenergic medication or a direct pudendal stimulation [67]; however, these attempts are mostly not very successful. The surgical options are focused on the increase of outlet resistance, either at the site of the bladder neck itself or at the external sphincter. Surgical techniques, such as bladder neck suspension [63], fascial sling (at the bladder neck or at the external sphincter) [49], open bladder neck reconstruction [11, 74], artificial sphincter implant (at the bladder neck or at the external sphincter), and periurethral injection with a substance, are the different options to consider [1, 10]. From all these options it must be mentioned that the periurethral injection of different substances has some good initial effect but no good long-term effects. Implantation of an artificial sphincter in very young children is not a first-choice treatment because of possible technical problems [55]. In addition, increasing the bladder outlet resistance in children with a neuropathic bladder dysfunction at that time with a good and highly compliant bladder can turn the bladder into a low or non-compliant bladder [21]. In our own patient population 4 of 36 children developed a high-pressure, low-compliant bladder after surgery at the bladder outlet and required additional bladder augmentation.

A final option may be a bladder neck closure and a creation of a catheterizable stoma. This technique was initiated and popularized by Mitrofanoff et al. and is still a very good solution in wheelchair-bound children or in those who are dependent on others to be catheterized.

Very obese children or children with manual uncoordination benefit from the creation of a continent, catheterizable stoma at the abdominal site (Fig. 6), especially wheelchair-bound girls. The abdominal site of the stoma site distracts from the genitals and it improves significantly their quality of life [26, 56]. Mitrofanoff et al. initially described the creation of a catheterizable stoma using the appendix, but more recently also ileum, stomach, or colon are being used, depending on the tissue used for augmentation. In addition, it should be re-

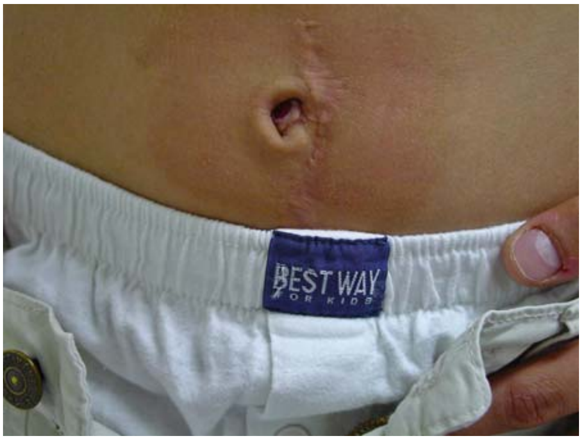


Fig. 6. Umbilical stoma. Obese children or children with manual discoordination will benefit from the creation of a continent catheterizable stoma at the abdominal site.

membered that to achieve bowel continence, the in situ plication of the appendix in the cecum can provide a channel to perform antegrade enemas (antegrade colonic enemas, ACE). Figure 6 shows how ACEs work and how the stoma can be located next to the umbilical stoma.

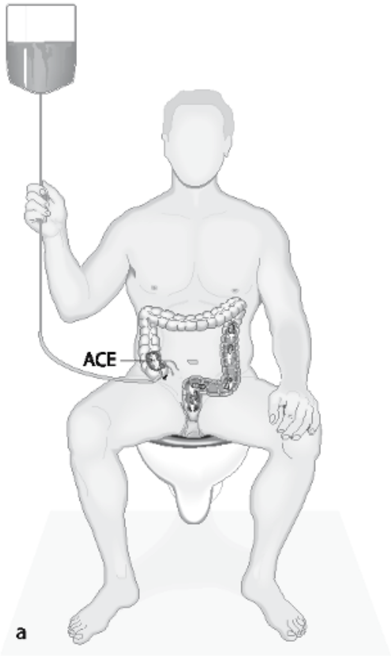
45.10
Vesicoureteral Reflux

Fifty percent of all children with neuropathic bladder dysfunction and congenital spinal dysraphism have or can develop vesicoureteral reflux [37]. It is emphasized that the occurrence of vesicoureteral reflux is a reflection of increased intravesical pressure; therefore, the first goal should be to perform a videourodynamic investigation and take precautions to lower the bladder pressure before considering specific treatment options for the reflux (Fig. 4) [4].

Ureteral reimplantation eventually leads to a higher incidence of stenosis, as the bladder muscle and the bladder wall is much thicker. Subureteral injection is insufficient without appropriate bladder pressure and capacity management. It is therefore recommended to observe low-grade reflux especially in the absence of recurrent urinary tract infections [37].

45.11
Latex Allergy

Children with spinal dysraphism have a very high tendency to develop latex allergy. Latex is a milky fluid from the rubber tree, *Hevea brasiliensis*. It is the basis to produce natural rubber; however, other chemicals need to be added (antioxidans, accelerators, conservatives) to make the strong, elastic, and stable end product: rubber.



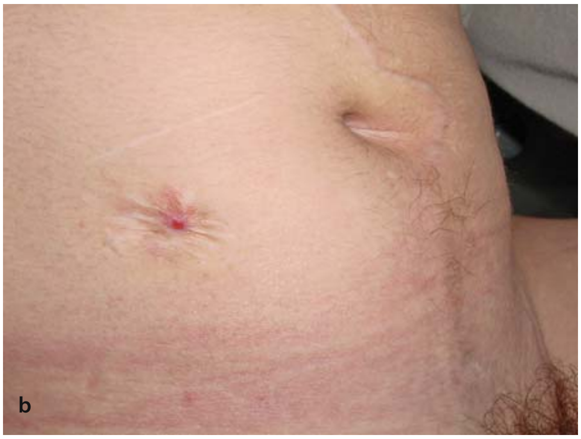


Fig. 7. Antegrade colonic enemas (ACE). a Scheme shows how ACE and an appendicocecostoma are working (to achieve bowel continence, the in situ plication of the appendix in the cecum can provide a channel to perform antegrade enemas. b Demonstration of where the appendicocecostoma can be located (besides in the umbilical stoma towards the bladder) at the abdominal skin level

There are two types of allergy: type I and type IV. Allergic contact eczema (type IV) is T-cell mediated and caused by the chemical additives [75]. This reaction is delayed and will only occur at the site of the contact.

Type-I allergy is IgE mediated and is caused by the proteins of the latex self. The symptoms will come up shortly after the contact and can be local or generalized. General symptoms can occur at the site of the skin (edema, erythema, itching, urticaria), eyes (edema of the sclera or eyelids, erthema, tears), nose (congestion, running nose, itching), mouth (edema of the lips, tongue, throat, uvula), cardiovascular system (hypotension, heart failure), lungs (bronchospasms, respiratory block), abdominal pain, and nausea.

Typically for a type-I allergy is that it starts 30–45 min after induction of anesthesia and beginning of the operation. There is difficulty to ventilate the patient, and it is as if there is a collapse of the lung. It is of the utmost importance to remove as quickly as possible all latex material, to give epinephrine, high dosage of corticoids, an H1 and H2 antagonists, bronchodilators, nonsteroidal anti-inflammatory substances, and to stop the surgery until full recovery of the cardiorespiratory situation.

The exact cause of the development of this allergy is not known. Capriles-Hulett have found in children with spinal dysraphism who had never had any surgical intervention that these children never develop latex allergy [14]. The risk of developing latex allergy increases with the number of surgical interventions, such as placement or changing a ventriculo-peritoneal shunt. Diagnostic screening can consist of the child playing with a balloon or a latex surgical glove during physical exam. If the child suddenly sneezes or starts coughing, he can be suspected of having developed latex allergy [68]. Also, further exam with determination of the total serum IgE and latex-specific IgE can confirm the diagnosis [86].

It is now recommended to perform all surgical interventions in children with a neuropathic bladder dysfunction in a latex-free environment from birth [68].

45.12
Bacteriuria

Children performing clean intermittent catheterization will develop mostly asymptomatic bacteriuria. If it's associated with pyuria and/or incontinence, the bacteriuria might develop into a urinary tract infection. Only in the situation of vesicoureteral reflux it is recommended to start an antibiotic or antiseptic prophylaxis [58].

45.13
Renal Development

One of the most important tasks of pediatric urologists following an up a growing child with congenital spinal dysraphism is ensuring a normal development of renal function. Elevated detrusor pressures and recurrent urinary tract infections are the primary risk factors, and threats for renal deterioration can be prevented by appropriate care of the lower urinary tract [71]. In addition to the high-pressure bladder, the situation of vesicoureteral reflux may aggravate the danger. It is therefore very important to follow these children regularly performing at least yearly a urodynamic investigation, and renal scintigraphy with MAG-3 combined with Cr-51 EDTA to determine the glomerular filtration rate (Fig. 3) [62, 77]. In unstable bladder conditions it is recommended to perform at least twice yearly an abdominal ultrasound, and in stable bladder function a yearly ultrasound remains recommended [20, 80].

It is stated that during puberty, the incidence of renal damage increases; however, it is unknown if this is due to the hormonal changes, to the physical changes (eventual spine deformity), to the reduced control of parents and the lower compliance of correct intermittent catheterization intervals and techniques (poor bladder management), or to the bladder augmentations (bowel) in this age group.

Similarly to the incidence of renal scarring or renal damage, the incidence of renal hypertension increases. It is unknown if other factors of neuropathic dysregulation may have an influence on the occurrence of hypertension.

Patients going into renal failure will have supplementary challenges to the dialysis and eventual renal transplantation because of the very probable unsafe bladder, the physical malformations (vertebral, kyphosis), the immunosuppressants, and with the bowel augmented bladder, the higher operative risk, and higher incidence of latex allergy. As there are only few data reported on renal transplant in patients with spina bifida, it is advised to make decisions on a strictly individual basis.

45.14
Bowel Management

The management of fecal elimination is also a significant challenge to patients and doctors. In the general concept of treatment, it should be emphasized that the caretakers must aim for independency of the child with spina bifida. Due to the neuropathic impairment of the bowel, constipation is the rule. Bladder and bowel management should be approached together. It is well known that uncontrolled bowel management can lead to bacteriuria and urinary tract infections.

As it should be the general goal to keep spina bifida children out of diapers, it is important that they have no accident inbetween voluntary and planned bowel emptying. Dietary precautions alone are insufficient to regulate bowel control. Digital evacuation or glycerine suppositoria may work in some children, but if daily enemas are feasible, this might be a viable long-term option; however, in children with insufficient pelvic floor muscles, the retrograde enema may not work, and the creation of a continent catheterizable antegrade enema stoma (ACE) is the option of choice of most patients (Fig. 7).

It takes 15–30 min to completely empty the large bowel with 200–500 ml tap water and is recommended to be done daily or every second day. This technique is now widely accepted and has been proven in the long term a significant improvement of the quality of life in children with neuropathic bowel problems [41, 45, 66].

45.15
Precocious Puberty, Sexual Function, Sexuality and Fertility

The first and principal rule is that pubers, adolescents, and adults with spina bifida have the same sexual desires, fantasies, and wishes as the general population without spina bifida. It is therefore necessary to respect their sexual life and wish for fertility, and it should be part of the general approach of these children throughout their development. Medical caretakers in cooperation with a multidisciplinary team should take an active role in developing normal social and sexual confidence. It is, however, very difficult to respect sexual privacy and development of their sexual identity, as these children are dependent on others for normal daily living in terms of bladder and bowel control [83, 84].

The incidence of an onset of precocious puberty is 30% in children with spinal dysraphism [36]. Occasionally the persistent hydrocephalus is the cause of this early onset; however, very often a direct cause is not found. It is especially girls who start to menstruate before the age of 10 years who develop, from a psychological aspect, significant problems. It is therefore recommended to screen for early-onset disease at puberty and to postpone the puberty by administering a Gn-RH analogum. Not only psychological problems, but also important bone deformities during pubertal changes, can be prevented or anticipated when puberty is delayed and controlled [15]. The pediatric urologist is frequently one of the first persons to discover early hormonal activity by examining the child during urodynamic investigation and observing pubic hair growth.

For a long time sexual functions were of little concern, because the care of live-threatening neurological and urological impairment in these children was unable to ensure long-term, stable situations; however, these children become adolescents and adults, and sexuality and fertility is now a subject of importance to patients with spina bifida [18]. When children are brought up and integrated in normal schools and social life, their self-image can be excellent compared to that of their peers – with one exception, however: sexuality [33]. It is therefore very important that pediatric urologists start open discussions with the teenaged children and their family or caretakers, as it is important to educate them and respect their sexual desires.

Another problem is the possible discrepancy between sexual desire, sexual sensation, and orgasm. Girls or women with neurological impairment below L2 are believed to have normal sensation; however, <20% of those with a lesion above L2 have normal sensation and orgasm capability [18]. In boys or men erection and ejaculation is the most bothersome problem. Normally the pudendal nerve (sacral origin) is responsible for the afferent genital sensation and for the efferent orgasmic contractions of the striated pelvic floor muscle. There is no doubt that most spina bifida patients lack these functions. The sympathetic, thoracic, and parasympathetic sacral nerve fibers form normally the pelvic plexus. Via cholinergic parasympathetic neurotransmission and induction, a relaxation of the smooth muscles, and therefore genital vasocongestion, occurs. During normal orgasm noradrenergic sympathetic neurotransmission induces emission via smooth muscle and expulsion via striated muscles. Two-thirds of the spina bifida patients with neurological impairment below Th10 report having erections, and only one-eighth of those with a lesion above Th10 also have erections; however, the erections are not necessarily correlated with sexual arousal. Intracorporal injection treatment is the most efficient treatment option [43]. Oral medication, as with sildenafil, has been reported to have various success and must therefore be individualized [59, 60]. Penile vibratory stimulation results in approximately 70%, and although specially (“medically”) designed equipment is available, the readily available vibrators in the sex shops have shown to have good success. Rectal probe electroejaculation produces an ejaculation in 75% of the patients; however, in patients with incomplete cord lesions or with intact pelvis sensation, general anesthesia is required. The electroejaculation should only be attempted in these patients who failed to respond to penile vibratory stimulation.

Fertility and possibility of paternity is then another difficult subject in spina bifida patients. In females, fertility is thought to be normal; however, a higher incidence of neural tube defects (especially in obese spina bifida women) and pelvic deformities (premature labor and increased risk for Caesarean section), together with the increased risk of urinary tract infections in an eventually ileal augmented bladder, makes it obvious that pregnancy is not a straightforward situation [69]. In spina bifida men, most of them are azoospermic on sperm analysis and may have Sertoli cell only on testicular biopsy. In some situations, poor semen quality has been associated with infrequent ejaculation [30].

45.16
Tethered-Cord Syndrome

Children born with occult spinal dysraphism have a typical primary tethered cord syndrome; However, after neurosurgical closure or surgery, scar tissue formation can cause a secondary tethered cord syndrome. This scar tissue formation and fixation of neural tissue can cause peripheral neural problems especially when the child grows fast (3–4 years and 8–10 years), because the conus medullaris elongates at that time. Urological symptoms and problems [34], with or without walking disorders, and a difference in the evoked potentials of the pelvic floor, are signs of such a syndrome [7]. The diagnosis of a tethered cord syndrome can be made by magnetic resonance imaging of the spinal canal, but the indication for neurosurgical removal of this scar tissue formation should be done on the basis of the clinical symptoms [48]. It is unclear and still debated if early neurosurgical intervention can prevent bladder function complications.

Foster et al. have reported that early intervention in the situation of a lipomeningocele (before the age of 18 months) is recommended and can prevent or reverse urological problems [27].

Close observation of the urological situation is recommended to “clinically” detect a tethered cord syndrome and can protect the bladder function worsening by a neurosurgical intervention [31]. Khoury et al. have reported in a large series that detrusor hyperreflexia can be reversed in more than 50% of the children [38].

45.17
Conclusion

Being born with myelomeningocele is a life-long crusade for the child and for the parents and siblings, who are often forgotten. It is a never-ending responsibility and impairment of quality of life. In addition, the medical care of patients with spinal dysraphism is a multidisciplinary specialized challenge and is not a simple and straightforward issue; however, there is more than just medical care: as much as possible, information to the family or caretakers is essential and, as soon as possible, to the children. Lack of adequate information and the ability to choose treatment options results often in lack of compliance of treatment. Doctors sometimes think they know what is best for the patient, but in reality it is only the patient who knows what is best for him. Medical caretakers must also try to achieve independence of the patient as much as possible. It is a wrong perspective that “others” can take better care of the child with spina bifida. As soon as other children achieve bladder and bowel control, the goal of medical caretakers should be to make these children also dry for bladder and bowel control, so that they can be socially integrated. If they are able to join normal school it has been shown that these children are happier and perform much better socially than if they would grow up in an environment with only physically or mentally disabled patients.

Renal failure and complications are still the most common cause of death in all age categories. Early intervention, regular diagnostic examination, and patient education are most likely to lead to the most successful outcome. From a pediatric urological point of view, it is very important to introduce intermittent catheterization as soon as possible to familiarize the patient and caretakers with this technique. In addition, the pediatric urologist must also treat the impaired bowel function and must be one of the first to bring up the subject of sexual identity and development. Of course, there is more, and only together with a multidisciplinary team consisting of pediatricians, social workers, urotherapists or nurses, neurosurgeons, orthopedic surgeons, physiotherapists, and all those wanting to devote time and care to these children and their families, can the team make a difference. Working as a team, the impaired quality of life of a child born with spina bifida can be decreased, and one can significantly contribute to make these children and their families happy in society.

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Neuropathic Bladder Dysfunction and Quality of Life

46

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46.1
Introduction

Quality of life (QoL) is a simple term that means: “How good is your life for you?”.

Assessing QoL means to evaluate the level of personal satisfaction for every aspect of life, such as social, professional, relational, sexual, and psychological issues, personal values and aspirations.

This is not a simple task to determine, as everyone defines and perceives differently from others what he/she considers to be a good quality of life, depending on geographical, socio-economical, religious, cultural and personal factors.

Evaluating Qol in the paediatric population is a particular topic of concern because of the difficulties of children, especially younger ones, with communicating, comprehending the issue and actively collaborating.

Most studies concerning QoL assessment in children are based on parental questionnaires only, although a multimodal approach, including questionnaires for both parents and collaborating children, is preferable, as subtle problems unseen by parents may be difficult to uncover.

When discussing about QoL in children with neuropathic bladder dysfunction (NBD) we generalize a pattern of “bladder paralysis”, applying it to patients with different clinical presentations and associated handicaps.

In most cases, paediatric NBD is congenital and spina bifida is the most frequent cause. Besides vesical dysfunction, patients with spina bifida present associated handicaps, including loss of mobility and sensation below the affected neurological level, decreased fine-movements skills, impaired bowel control, hydrocephalus, orthopaedic anomalies, such as scolosis and hip congenital luxation, and, sometimes, mental retardation.

Children with congenital malformations and physical handicaps, since the newborn period, experience a chronic illness status which is characterized by repeated examinations, prolonged hospitalizations and multiple interventions.

In a norm-fashioned world, patients born with severe congenital pathologies face major frustrations, as chronic disabilities determine a negative impact on many aspects of life, creating not only specific illness demands, such as self-care, mobility and hospitalizations, but also affecting psycho-social and family life, academic achievements and employment [1].

Chronic handicaps are associated with higher rates of psychological maladjustment, approximately twice as much as those observed in control populations [2, 3].

Hirst et al. [4] showed that, rather than the type of disability itself (e.g. cerebral palsy or spina bifida), it is the combination of functional loss (e.g. walking problems and incontinence) and dependency on others that is mostly responsible for a poor outcome.

Ambulatory status clearly influences self-esteem, body image and sense of independence, although Moore et al. [5] reported no differences about self-concept outcome in walking vs wheelchair-bound patients. Other studies have proved that girls with spina bifida had worst psychological, relational and social outcome than boys, thus suggesting that physical appearance more strongly influences self-esteem in females than in males [5].

How individuals with disabilities value themselves (self-esteem) and view themselves (self-concept) are considered central aspects of psychological functioning. Children with NBD are thought to be at an increased risk for low self-concept and low self-esteem, given their physical disabilities and functional impairment.

Higher rates of psychological problems, such as depression, low self-esteem, and social isolation, have been reported by Breslau and Marshal [5], and even an higher frequency of suicidal tendencies by Dorner [6] as well as others [7, 8].

Several studies have proven problems in cognitive and academic functioning and social disadvantages [8, 9], such as decreased opportunity for peer relationships, prolonged dependency on parents and decreased community acceptance [10, 11].

Tin and Teasdale reported that social interaction patterns differ qualitatively and quantitatively from those of peers [12], as these patients are often interacting with few people for long periods and have less contact with peers of the opposite sex.

In addition to functional impairments, other factors, such as patient and parental adjustment to the handicap, influence QoL.

Viemero and Krause found that the person's ability to cope with everyday life had a bigger impact on QoL than the disability itself [13].

Barakat and Linney reported a clear relationship between available resources [14], such as maternal and social support, and better adjustment outcome for both the mother and the child.

Similarly, Sloper and Turner showed that in a sample of families of children with severe physical disabilities [15], the most vulnerable families (i.e. those with considerable unmet needs or with economical difficulties) found it hard to obtain help, had less resources available and were more likely to take a passive approach to dealing with problems.

Family resources have a direct effect on QoL; therefore, measuring the needs of parents is an effective way to devise interventions that can improve the psychological and social well-being of the child [16].

In the final analysis, evaluating the impact of bladder dysfunction alone on the QoL of these patients, independently from other associated handicaps, is not easy. Nevertheless, a liaison between the QoL and the type and the severity of neurological impairment has been clearly demonstrated by Pit-ten Cate et al. [16].

46.2
Functional Types

Neuropathic bladder dysfunction can be classified schematically into two functional types:

1. Retentionist bladder (failure of bladder emptying function), which is generally associated with sphincteric hyperactivity determining high intra-vesical pressures and incomplete bladder emptying.
2. Incontinent bladder (failure of urine storage function), which is characterized by the deficiency of continence mechanisms (low leak-point pressure) determining low intra-vesical pressures, and continuous urinary leakage with minimal urinary residual.

46.3
Retentionist Bladder

In the first type (retentionist bladder), an augmented risk of urinary tract infections (UTIs), upper urinary tract dilatation, renal damage and stone formation is observed; therefore, complete bladder emptying is mandatory to be obtained several times during the day in order to reduce these risks. Starting in the first months of life, scheduled clean intermittent catheterizations (CIC), antibiotic prophylaxis and anti-cholinergic treatment are the most appropriate therapeutic strategy; therefore, these patients experience, since the newborn period, hospitalizations, repeated examinations, chronic treatments and invasive procedures negatively affecting the QoL of children and parents from the beginning.

The use of sterile catheterizations to achieve complete bladder emptying was proposed by L. Guttmann in 1966, but it was Lapides in late 1970s to propose the revolutionary innovation of CIC, which has since gained increasingly more popularity. Patients and families must learn to incorporate catheterization into daily routine and be able to perform the procedure four to six times a day.

Male patients can perform CIC both in seated and standing position, although urethral length may sometimes determine difficulties with catheterizations and even urethral injuries.

In female patients, CIC are usually easier to perform because of the shortness of the urethra, but a recumbent position is necessary in most cases.

Children from about 6 years of age are generally considered to have adequate cognitive and manipulative skills to catheterize themselves (self catheterization, SC). Until the child is ready and able to correctly perform SC all alone, this has to be done by parents or caregivers.

In general, any method of self-management, such as SC, is described to physically and psychologically benefit the children, granting more freedom and privacy and increasing body image and self-esteem [17].

Although catheterization is a well-established and effective management of neuropathic bladder, there are many practical, social and emotional challenges faced by these young patients and their families, both in learning and routinely performing this procedure.

A recent work investigated the social and psychological impact of CIC in 40 English families with children and adolescents affected by NBD [18], showing that the majority of the children thought that the decision to perform CIC was taken by the doctor in agreement with the parents, and only a few of them knew the reason and the objective of practicing CIC.

It may be difficult to motivate these young patients to perform CIC, as the greatest benefit (long-term good renal function) is "invisible" for these children who are unable to think ahead to their future. however, in most cases, they understand that CIC and SC are better than any other alternatives and seriously strive to quickly reach complete autonomy.

Those who can effectively manage CIC claim to be satisfied with the procedure; however, most people find it hard to speak about catheterizations to people other than close friends and family members, and prefer to hide the problem.

These young patients often feel anxiety about damaging or hurting themselves by “doing it wrong”. This highlights the need for professional and attentive support in teaching the procedure, choosing comfortable settings and using tutoring and teaching resources such as dolls, diagrams, books and videos [19].

School-time CIC have proved to be particularly challenging. A full collaboration between the paediatric team, family and school staff is necessary in order to provide these patients with adequate privacy, hygiene and access to appropriate facilities, as well as skills and strategies for disclosing information or addressing questions from peers [20].

Opportunities to meet other patients using CIC are highly encouraged, as sharing experiences is strongly demanded by children and families themselves.

Children with chronic diseases have an augmented risk to develop latex allergy (up to 45% in patients with myelodysplasia), related to the recurrent exposure of body surfaces to medical devices containing latex, throughout the entire childhood.

Reactions range from milder forms, such as contact dermatitis, to more serious complications, such as anaphylaxis and cardiac collapse.

Presently, only latex-free devices should be used for patients undergoing multiple urological procedures since the newborn period, including gloves, catheters, crib pads, and bottle nipples, which are all potential sources of hypersensitivity.

Recent technical developments have drastically improved the quality of modern catheters and facilitated their use. The introduction of single-use self-lubricating catheters made catheterizations more feasible, and the use of modern and almost hidden collecting bags (such as those that can be fastened to the tights) has improved social and relational outcome.

In younger children, when trans-urethral CIC is particularly difficult, excessively painful or too risky for urethral integrity, or when the child and/or the family are not reliable, a urinary diversion, such as a temporary vesicostomy, may be performed in order to obtain a complete and safe bladder emptying. This procedure preserves the bladder filling/voiding cycle, as continuous urinary leakage from the abdominal stoma begins only at critical volume, thus allowing the bladder to increase its capacity with time and protecting the upper urinary tract.

The abdominal stoma may alter the body image of the child and worry the parents; however, in most cases this temporary option is well accepted, as these young patients hide the lower abdominal stoma using the same diapers as all other infants of the same age.

Vesicostomy can be safely closed only when a complete bladder emptying can be achieved or when either the child or the family can adequately perform CIC [21].

Older children, when trans-urethral CIC is particularly painful or difficult (i.e. in wheelchair-bound patients or urethral anomalies), may benefit from a catheterizable continent urinary diversion, such as the Mitrofanoff vesicostomy.

In 1980 Mitrofanoff described the use of the appendix as a catheterizable conduit between the bladder and the abdominal wall, and ever since the Mitrofanoff procedure has been applied to various tissue, such as reconfigured or tapered ileum, stomach, colon, ureter, tubularized bladder, and even fallopian tube [22, 23].

This procedure represents a major surgical and functional innovation and has gained increasingly more popularity, as it has revolutionized the management of urinary incontinence and bladder dysfunctions both in children and adults, significantly improving the QoL of these patients.

The abdominal stoma makes catheterizations easier and socially more acceptable, as the inconvenience and/or embarrassment of disrobing at school or in other places is avoided. This is particularly beneficial for non-ambulatory patients who do not need to be transferred from their wheelchair.

The creation of a catheterizable channel as an alternative access to the bladder is recommended for all patients undergoing a bladder neck procedure or an augmentation cystoplasty, as these types of surgery can increase the challenge or preclude a reliable emptying through the urethra.

The use of the appendix has stood the test of time, and most authors consider it as the first-choice tissue. Its straightforward configuration, the supple and solid muscular backing, and the adequately large lumen provide an advantage over reconfigured or tapered tubes, as no suture lines introduce wall irregularities that may interfere with CIC.

Overall functional outcome is good, but complications are not rare; therefore, patients must be carefully selected, as this procedure is indicated only in reliable and sufficiently autonomous patients with adequate manual skills and mental development.

Woodhouse reported a 94% continence rate in 34 patients using the Mitrofanoff procedure [24], of whom 23 underwent bladder neck closure.

Stomal or bladder level stenosis of the conduit may determine difficulties with catheterization requiring surgical revisions, whereas stomal prolapse is less frequently observed.

Catheterizations may sometimes be painful, because of chronic irritation of the conduit from catheter rubbing. In our experience, the use of appendix determined a better functional outcome than utilizing the reconfigured ileum (Monti procedure): complications, such as difficulties with CIC requiring surgical or endoscopic treatment (10 vs 26%) and stomal urinary leakage (5 vs 26%), were more rare in the appendix group.

Although the Mitrofanoff procedure may impair body image, literature data shows an improved psychosocial outcome, as these children and adolescents reported an amelioration in their self-confidence, body control and feeling of independence [25].

Positioning the stoma at the umbilicus may determine a better aesthetic outcome than right lower abdominal quadrant stoma; however, the latter enables a more complete bladder emptying, as the catheter enters the bladder horizontally and drains the urine more efficaciously.

The Mitrofanoff vesicostomy enables these patients to have a more active life and achieve better living standards, including the possibility to practice social and sports activities which were precluded before.

Patients with NBD and associated impaired intestinal control may also benefit from the Malone antegrade continence enema (MACE) procedure [26], and some authors recommend to reserve the appendix for this procedure, although synchronous use of appendix for both Mitrofanoff and Monti procedure is possible when long appendices are found.

In patients with bowel impairment, especially wheelchair users, standard enemas are difficult if not impossible to perform: providing a continent catheterizable access to caecum can make these children clean, thus significantly improving self-esteem, independence and social integration.

The management of urinary incontinence requires a concomitant program for faecal continence; therefore, gaining a good bowel control with MACE procedure will stimulate the child to reach urinary continence as well.

Patients with a small and poorly compliant bladder may benefit from an augmentation cystoplasty in order to obtain a compliant and low-pressure reservoir. This major surgery requires a long post-operative hospitalization and is complicated by life-long problems, such as mucus production and electrolyte absorption; therefore, augmentation cystoplasty should be performed only in carefully selected patients only when an adequate pharmacological treatment with anti-cholinergic drugs has proved to be unsuccessful in order to increase bladder compliance and capacity.

In the past 30 years, oxybutinine alone, and in association with CIC, proved to be quite effective for this purpose, thus reducing the need of urinary diversion.

Recently, Botox proved to be quite effective when oxybutinine and CIC failed to improve bladder capacity and compliance; however, long-term results are unsatisfactory, as this procedure has to be repeated every 6 months [40].

Several techniques have been described for bladder augmentation, including detrusorectomy, which requires short hospitalization and obviates the incorporation of intestine into the urinary tract; however, this procedure is indicated only in selected cases and long-term outcome is poor.

Various techniques using different bowel segments (stomach, ileum, caecum, and sigmoid) have been described.

The incorporation of bowel segments into the genitourinary tract is complicated by fluid and electrolyte absorption leading to metabolic complications, such as hyperchloremic metabolic acidosis; however, in children, these problems are less frequently observed than in adults.

An increased frequency of UTIs and urinary stones formation is commonly described, which is due to urinary stasis secondary to dehydration, incomplete reservoir emptying, mucus production and frequent colonization with urea-splitting organisms.

Mucus production is a serious threat to bladder emptying and determines an augmented risk of UTIs, lithiasis, urinary retention and bladder perforation; hence, patients and caregivers must be taught to perform regular irrigations of the reservoir, in order to adequately evacuate the mucus.

Patients with renal insufficiency and chronic acidosis are not good candidates for enterocystoplasty and may benefit from gastrocystoplasty, because of the acid secretion potential.

The use of the stomach has the advantage of a lower mucus production and of sparing the intestine; however, these patients need life-long anti-acid or proton-pump-inhibitor treatment.

Gastrocystoplasty may be complicated by haematury-dysury syndrome, peptic bladder perforation, untreatable pelvic pain and, in incontinent patients, also perineal burns due to acidity of the urine. For these reasons, its popularity and utilization has significantly decreased.

Development of late uro-intestinal malignancy after bowel incorporation into the urinary tract is a constant, long-term hazard, as a low but still distinct risk is reported [27, 28]; therefore, adequate annual follow-up is advocated, particularly for enterocystoplasties.

46.4
Incontinent Bladder

In the second group of NBD, the incontinent one, the risk of urinary tract infections (UTIs) and renal impairment is low, as the upper urinary tract is protected by low vesical pressures and continuous urinary leakage; therefore, frequent clinical and laboratory controls, medical treatment and invasive procedures, such as CIC, are usually not needed for these patients.

In the first years of life, the use of diapers does not differentiate these patients from their peers, and continuous loss of urines does not affect their QoL, as urinary continence, being a social convenience, is not an expectation for infants and young children.

When school age has been reached, these patients and their families start to make comparisons with normally continent school peers, discovering that urinary incontinence represents a problem and beginning to consider it as a handicap: at this point, achieving continence becomes a priority issue, and a solution is strongly demanded.

Lie et al. showed that urinary incontinence in school-age years is perceived as one of the most stressful challenges [29], as both the patients and the parents rated it even worst than other handicaps, such as impaired motor function.

The social stigma of urinary incontinence can make disclosure and self-acceptance of the problem more difficult and deteriorate QoL keeping these patients from fully participating in social [30], school and sports activities [31].

Pharmacological treatment both with anthicolinergic drugs and imipramine may be the first choice to attempt to reach continence. Unfortunately, pharmacology alone is quite ineffective in giving continence to this group of patients.

Many surgical options have been proposed to treat sphincter deficiency, but to date no operative technique represents the gold standard, as none of them can restore the complex neuromuscular mechanisms involved in the dynamic phenomenon of continence.

Although bladder neck endoscopic injection of bulking agents failed to obtain long-term continence rates comparable to those of open surgery, this outpatient procedure does not significantly modify the anatomy of vesico-urethral junction and has the advantage of being repeatable; hence, we highly recommend this option as a first approach.

Continence surgery is an extremely challenging and difficult task, complications are potentially severe and outcome is unpredictable.

When the intervention is successful and “social” continence is achieved, a complete bladder emptying is difficult to obtain and CIC may become a necessity in order to avoid urinary retention, upper urinary tract dilatation, UTIs, urinary stones formation and renal damage; hence, the QL of these patients will drastically change after the intervention, as achieving continence will determine for the first time in their lives the need of a life-long care and follow-up, including strictly scheduled bladder emptying, prolonged medical treatment, and frequent clinical, laboratory and instrumental controls.

Patients and parents must be fully informed of all potential risks and, above all, must clearly understand that continence surgery will not heal the neurological lesion and will not restore the physiological mechanisms of continence, but will simply increase urethral resistances in order to achieve longer and socially more acceptable dry intervals.

Timing for surgery must be appropriately scheduled, and a careful selection of patients is mandatory, as the reliability and self-care abilities of the child and the family must be carefully assessed for a successful outcome.

If the child or carergivers are unable to correctly perform CIC, continence surgery is contraindicated, and leaving these patients incontinent but without risks for the renal function is the best option.

Bladder neck reconstruction, such as Young-Dees-Ledbetter’s technique, seems to have a good continence rate in exstrophic patients, but not as good in neuropathic children [32].

Kropp and Pippi-Salle procedures may determine up to 70% of continence rates [33]; however, these techniques significantly modify the anatomy of vesico-urethral junction. This may hinder a complete vesical emptying, determine potential difficulties with CIC and preclude other future treatment options.

Urethral suspension procedures are less invasive and may determine good functional outcome both in males and females, but long-term results are not as satisfactory, and difficulties with CIC may occur [34].

Artificial sphincter is presently the best option for selected and motivated post-pubertal patients with sufficient autonomy and normal bladder capacity and compliance, although frequent long-term complications are described [35]. Previous continence surgery that significantly alters the anatomy of the region is a contraindication to the use of artificial sphincter.

Over the years, many efforts to create a functional artificial bladder have been unsuccessful. In the 1990s major advances were made in the area of tissue regeneration and engineering, and these efforts are currently being undertaken for every type of tissue and organ within the urinary system. Atala [36] and Atala et al. [37] have shown that bladder tissue can be harvested and expanded in vitro for later bladder augmentation. Growth of all three bladder layers in this “seeded” technique has also been demonstrated [38, 39].

Although these techniques hold great promises, much is still to be learned, and routine clinical use remains a possibility.

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Measuring Quality of Life in Adolescent and Young Adults with Spina Bifida: Usefulness for Physicians Involved in Incontinence Management

47

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47.1
Introduction

The aim of the authors is to present the concept of health-related quality of life (HRQoL) in medical care and to determine how this concept can be applied for spina bifida (SB) patients especially for incontinence management research. Spina bifida is the most common congenital disabling condition in children responsible of sphincter disorders. Urinary and faecal incontinence are frequently encountered. Secondary issues from incontinence on HRQoL include psychological health, social relations, well-being, vitality, family functioning, self esteem, leisure and communication, all fields which are highly considered by patients, their families and physicians. Management of incontinence may vary according to the patient's and family's point of view. For the past two decades, major improvements have occurred in incontinence treatment especially in the surgical field justifying study of how they interfere with the HRQoL concept. The authors present firstly HRQoL at a conceptual and methodological level. Secondly, they discuss how this concept can be put into practice for SB patients considering the results of the literature and their own experience in management of these patients.

The sequelae of SB include decreased mobility, bladder and bowel incontinence, and neurosensory disabilities as well as social disadvantages such as decreased community acceptance and lack of a supportive peer network [1].

Before 1960, less than 10% of patients survived infancy, whereas presently that number exceeds 85% [2]. A number of longitudinal studies have assessed long-term outcome of individuals with spina bifida with respect to physical function [3], cognitive ability [4], psychosocial development and the impact on the family [5–7]. As regards the incontinence issues, the therapeutic pendulum has swung considerably, from recommendations for conservative therapy to lower urinary tract reconstructive surgery associated with faecal incontinence surgical management [8–11].

Given the uncertainty about the best management for an individual infant with SB, it has been suggested that "parental directives for care" might resolve some of the dilemmas that arise when health caregivers make judgements about their patients' future Quality of Life (QoL). This suggestion is in keeping with an increasingly heard request for more parental involvement in medical decisions. Nonetheless, in order to make rational decisions, parents need accurate prognostic information. These considerations suggest that SB has a significant impact on the health of individuals, as is broadly defined by the concept of HRQoL. Although physicians are intuitively aware of the impact of different chronic conditions on functioning and well-being, they need precise measures of these outcomes to routinely monitor the effects of their care on theses outcomes. Moreover, it has also been shown that children and their families do not view their health as negatively as do their physicians [1]. This suggests that HRQoL might be best understood from the viewpoint of the individuals themselves, rather than from the viewpoint of clinicians. As regards the papers about incontinence management in SB patients, improvement of QoL is often mentioned as an ultimate goal which can be reached with positive incontinence management; however, relations between continence and QoL as much as relations between determinants of continence and QoL have not been yet clarified.

We present issues resulting from QoL measure at a conceptual and methodological level. Then we review the most recent articles focusing on incontinence management and HRQoL in SB patients.

47.2
The Framework of QoL

In medicine, there are at least seven plausible goals that are irreducible to each other, namely to promote functioning, to maintain, or restore normal structure and function, to promote quality of life (QoL), to save and prolong life, to help the patient to cope well with her condition, to improve the external conditions under which people live, and to promote the growth and development of children [12]. Interest in QoL is on the increase [13]. A prominent impetus for QoL considerations has been the desire to compare outcomes from different efforts, alternative service programs for an identified group of people, or specific interventions for a health condition. There has been a call for new outcome measures that reflect a more holistic approach. Such an emphasis reflects contemporary views about the relation between mind and body, and acknowledges the critical link between physical and psychological health. The QoL measures may be of potential value in comparing outcomes in clinical trials, evaluating intervention, commissioning programs of care, assessing the outcomes of new treatments and in audit work; however, the concept of QoL is unclear. Firstly, the idea is that individuals have their own unique perspective on QoL, which depends on present lifestyle, past experience, hopes in the future, as well as dreams and ambitions [14]. Secondly, when used in a medical context, QoL is generally conceptualised as a multidimensional construct encompassing several domains. Reference to this concept is often made without delineating the theoretical and practical framework of this term. Definition has been given by the World Health Organisation (WHO-QOL Group), as *individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns* [13]. The QoL is by its nature an holistic concept, an attempt to describe how well or poorly life works at a particular point in time. It is a broad concept, incorporating in a complex way individual's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment [15]. Not surprisingly, being a relatively young endeavour, there is considerable diversity in conceptualisation and operational approach to QoL. It is important to bear in mind that QoL is a construct, and has no physical basis. It is not directly a measuring entity or instrument. A construct, such as QoL, is an organising concept that exists to guide its users. Observed variables are presumed to be tangible but imperfect indices of the underlying construct; however, a construct can never be fully put into operation by its measurements. There is always a figurative distance present between in which we are truly interested (e.g. QoL), and its measurements (e.g. responses to a set of items). There is widespread agreement that QoL is a multidimensional concept. Within this framework, QoL encompasses the domains of material, physical, social, emotional and productive well-being, each of which is further subdivided into sub-domains (Table 1).

Table 1. Multidimensional structure of quality of life according to WHO [42].

Domain	Facets incorporated within domain
Domain	Facets incorporated within domain
	Overall quality of life and general health
Physical health	Energy and fatigue Pain and discomfort Sleep and rest
Level of independence	Mobility Activities of daily living Dependence on medicinal substances and medical aids Work capacity
Social relationships	Personal relationships Social support Sexual activity
Environment	Financial resources Freedom, physical safety and security Health and social care: accessibility and quality home environment Opportunities for acquiring new information and skills Participation in and opportunities for recreation/leisure Physical environment (pollution/noise/traffic/climate) Transport
Spirituality/religion/personal beliefs	Religion/spirituality/personal beliefs

Wallander et al. stated that all definitions of QoL should be referenced to the general population both in their conception and operational measures [16]. The QoL as a construct is applicable to all individuals. No differentiation should be made between those who have specific health conditions, and no health condition. As an alternative to the QoL concept, the term health-related QoL (HRQoL), has become preferred by many [17]. The aim is to assess the impact of disease and treatment on the life of patients, in contrast to the effect of jobs, housing and school, components which are outside the purview of the health care system [18]. The HRQoL refers to quality of life as a result of a certain health. The assessment by a person of his or her own health functioning is called health status. To assess the HRQoL of a person not only is health status relevant but also the emotional evaluation of this health status by the person him- or herself; therefore, HRQoL is defined as a combination of health status and affective responses to problems in health status. The HRQoL can be expressed by two different measures: generic and disease specific [19]. Generic measures have been devoted primarily considering QoL applicable across all people. They represent the idea that no differentiation should be made between those who or do not have specific conditions and can be used whatever the conditions of the individuals. The low incidence of some conditions will preclude development of disease-specific measures. Among them, asthma, cancer, epilepsy have received most attention in childhood [14]. For children with many other conditions it is only possible to rate HRQoL using a generic measure. Generic measures are suitable to assess HRQoL regardless of the child's specific condition. Assessment of HRQoL in children poses specific problems. Children do not share adult views about the cause, aetiology and treatment of illness. They may interpret questions differently and adopt a different time perspective regarding the course of a disease. In addition, their abilities to use rating scales, understand the language, and generally complete lengthy questionnaires of the type used in adult work, may be compromised by age and cognitive development. The approach of QoL measure in children differs conceptually whether the focus is on: (a) the objective quality of the conditions in which the child lives; (b) the child's subjective satisfaction with their life; (c) some combination of the objective and subjective approaches; or (d) some combination of the objective and subjective perspectives in which specific domains of HRQoL are weighted by the child's values, aspirations and/or expectations [16]. These fine distinctions between objective and subjective values in representing HRQoL refer to the potential confusion between HRQoL and its determinants on which physicians can act in concrete terms (e.g. objective facets). Children are often regarded as unreliable respondents; however, children and parents do not necessarily share similar views about impact of illness and therefore there are calls to involve children more directly in decisions about their own care and treatment. Consequently, HRQoL measure in children requires specific considerations. In a recent review [14], the authors identified available generic and disease-specific measures to assess HRQoL for children with chronic illness. According to their criteria they conclude that only few HRQoL measures fulfil very basic psychometric criteria in children. Generic measures selected by Eiser and Morse are presented in Table 2 [14]. As an example, structure of CHQ-CF87 is presented in Table 3 [20].

Table 2. Selection of generic measure of health-related quality of life for children. (After Eiser and Morse [14]).

Criteria of selection	Results
Measures of QoL, health status or well-being	Generic measure
Children aged 18 years or under	Child health questionnaire [20]
Measures that include minimum psychometric properties (some reliability or validity data)	Paediatric QoL questionnaire [43]
Measures that include facility for completion by child or proxy or both	Health Utilities Index, mark 2 [44]
Single (generic or disease specific) or proxy measures	

Table 3. Structure of the Children's Health Questionnaire (CHQ–CF87; from [20]).

Dimensions	No. of items
Physical functioning	9
Social–emotional role	3
Social–behavioural role	3
Social–physical role	3
Bodily pain	2
Behavior	17
Mental health	16
Self-esteem	14
General health	12
Familiy activities	6
Family cohesion	1
Change in health	1

47.3

Measurement Properties in Health Indices

Tests and measures in clinical medicine or social sciences can be used for three purposes: discriminating between subjects; predicting either prognosis or the results of some other test; and evaluating change over time [21]. Discrimination, prediction and evaluation constitute the targets of HRQoL measure development. These characteristics of HRQoL instruments are not complementary and are actually competing. Other properties of HRQoL measure concern reliability, validity and responsiveness [22]. Reliability can be measured by serial administration of a test to a group of subjects whose status on the dimension being examined is believed to be stable. Validity refers to the extent to which a measuring instrument produces the same results as a gold standard, or criterion measure. Content validity refers to the completeness with which an index covers the important areas of the domain which it is attempting to represent. Construct validity is concerned with the extent to which a particular measure relates to other measures in a manner which is consistent with theoretically derived hypotheses concerning the concepts (or constructs) that are being measured. While demonstration of reliability and validity is sufficient for concluding that an instrument is useful for descriptive or predictive purposes, we must also have information about an evaluative instrument's responsiveness before we can confidently use it as an outcome measure in a clinical trial. Regardless of which method is chosen, the investigator must come to grips with the effect of random and systematic error on the power of the test. When large sources of measurement error are present, then beta error is increased and consequently the power of the test is decreased. If the power of the test turns to be too low, requiring an unattainable N to observe a desired effect size at a given level of alpha, then the index is not useful as an evaluative instrument [21]. These problems explain in clinical practice the development of disease-specific instruments to measure HRQoL especially for clinical trials.

47.4

Relationships Between Rehabilitation Goals, Treatment Strategies and QoL in Spina Bifida Patients

Specific issues pertinent to the ongoing comprehensive management of children dysraphism include prevention of complications, mobility, toilet training and management of the neurogenic bladder and bowel, skin management, health care maintenance, assessment of cognitive, language, and fine motor skills, provision of appropriate therapy to enhance gross motor, fine motor and communication skills, school and vocational integration, psychosocial adjustment to disability, family adjustment, recreation and vocational activities and transition to adolescence to adulthood. According to the theory of the goals of medicine [12], the only two goals that have final value for the patient are high HRQoL and a long life. All specific issues can be considered as determinants of HRQoL on which physicians and care givers can act in practical terms to improve HRQoL. Moreover, one major application of HRQoL instruments is to assess the outcomes of interventions for adolescents with chronic conditions and disabilities. On this basis it is important to ensure that all aspects of the outcome continuum be measured when considering new interventions so that the impact of treatment can be detected both on the health status of the individual, and also on their subjective HRQoL and consequently their adjustment to the disease. During the past decade, introduction of new surgical and medical treatments has greatly reduced the number of renal complications and incontinence problems in persons with SB; however, impact of these treatments on HRQoL has not been studied using validated HRQoL instruments, either generic or specific. In this new perspective, Parkin et al. [23] presented the development of a disease specific HRQoL for SB patients, and secondarily, Kirpalani et al. [24] reported the role of parental hope as determinant of QoL. Cate et al. [25], Padua et al. [26] and Sawin et al. [5] studied the relations between disability and QoL in SB patients with minimal reference to continence status as a variable in comparison to functional assessment. Articles which mention impact of incontinence management on QoL were presented by Bomalaski et al. [27] and Yerkes et al. [28]. For the first one, the issues focused on education level, living arrangements, employment and sexual relationships. Three groups of patients were distinguished according to their urinary management, intestinal conduit in early childhood, clean intermittent catheterization or micturition with straining or Credé manoeuvre. Continence were presented as complete, or with minimal or severe leakage. The authors concluded that there was no significant difference according to modalities of urinary management for the four domains studied. In contrast, Yerkes et al. [28] reported a high success rate of Malone continence antegrade enema in faecal incontinence management with significant improvement on some aspects of QoL. More recently, Moore et al. reported the results of their study on the impact of urinary incontinence on self-concept in children with spina bifida [29]. The authors concluded that continence is associated with better self-concept and incontinent girls present higher risk for poor self-esteem.

In recent articles [10, 30], a large review of medical and surgical therapeutic principles has been presented. As a basic premise, it is advocated that both urinary and faecal incontinence in organic conditions, such myelodysplasia, causes many people embarrassment, lack of self-esteem, psychosocial and familial disturbances or later vocational segregation. No physicians would disagree with these considerations; however, to our knowledge, this has not really been explored in the practical life of these patients. Moreover, we do not know exactly to what extent minimal leakage or complete dryness are ultimate gaols for incontinence management. Such consideration has very significant surgical implications. Many procedures have been developed to increase bladder neck resistance keeping possibilities of urethral intermittent catheterization [31, 32]. On the other hand, continent diversion through catherizable conduit has been devised including definitive closure of the bladder neck [33, 34]. There is much available data about functional results and complications with urinary continent diversion, but none reveal how patients feel themselves with diverted lower urinary tract and how they feel about the modification of their body image. As it has been proved that continent diversion is efficient in incontinence management, the impact of this procedure on QoL should be demonstrated. Trying to make the bladder neck both continent and catherizable has frequently led the patient through serial surgical procedures and finally significant persistent incontinence. Conservative incontinence management with medication and intermittent catherization has allowed an acceptable social continence for many patients with persistent leakage. Even if their condition could be improved with bladder surgery, they give preference to conservative management to avoid major surgery and the risk of secondary complications. This fact indicates that the opinion of the patient on his own HRQoL does not follow in parallel his functional status. Patients with myelodysplasia often encounter lack of bowel control and need assistance in faecal cleanliness. Consequently, concomitant surgery including bladder surgery and some form of antegrade colonic enema (ACE) procedure has been proposed [35]. On many occasions, ACE procedure has been presented as a factor to improve HRQoL in patients with severe faecal disorders [36]. Many reports have brought encouraging results on improvement of constipation and faecal cleanliness [37, 38]. As a basic consideration, it seems to be logical to confirm the clinical benefits through improvement of HRQoL as it has been previously defined and developed for clinical use. Moreover, standardised questionnaires with available translation in several languages would permit comparison of the results over different countries and teams. This cross-cultural adaptation needs a several-step process from translation and back-translation to committee review, pre-testing and weighting of scores [39].

47.5
Perspectives for Research

The HRQoL measure is becoming increasingly relevant especially in conditions that may involve the general status of patients. This index is rarely described in SB patients, and most of the studies do not take into account specific issues of incontinence management with which physicians are confronted. Firstly, relations between urinary and faecal incontinence and HRQoL should be stated. Then the effects of management, medical or surgical, on HRQoL should be established. Specifically, the role of surgical approaches with bladder reconstruction, with or without Mitrofanoff or Malone procedures, should be explored under the angle of HRQoL. The development of a disease-specific HRQoL measure for use with SB has been proposed by Parkin et al. [23]; however, we must keep in mind that clinical conditions encountered in SB can be seen with various diagnoses, such as sacral agenesia, ano-rectal malformation or cloaca, paraplegia secondary to trauma, medullary tumour or infection or failed exstrophy repaired. Impact of treatments, especially surgical management, should be taken into account with regard to both continence status and all domains of HRQoL. The HRQoL instruments are various and do not reflect to the same extent the domains of QoL. Generic measures still keep interest for chronic conditions to evaluate the holistic complex of QoL but specific questionnaires should be considered for clinical trials.

47.6
Conclusion

The relationships between traditional clinical variables, functional measures, impact of events and HRQoL measures should therefore be adequately understood [40]. Although there is growing interest for QoL measure in clinical practice and research, QoL remains a broad-ranging concept that is difficult to define and measure, and therefore can often be misused. A misuse of the concept indicates inconsistency between what is being measured and labelled as QoL, e.g. measuring symptom status and not QoL [41]. The general rehabilitation goals for children with spinal dysraphism include improvement of function and independence, improvement of the child's development experience to the extent possible and improvement of QoL. Results of surgical interventions especially for incontinence have been widely reported in the literature; however, to our knowledge, the effects of surgical management of incontinence on HRQoL in SB patients have rarely been reported. Relationships between continence and QoL should be explored from the perspective of the child and his or her family, and the proxy, in order to refine management strategy.

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Follow-up in Children with Neurogenic Bladder Dysfunction

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48.1
Introduction

Neurogenic bladder dysfunction is a common problem in urology practice that has a wide spectrum of clinical presentations. The etiology is varied, including congenital defects (spina bifida, sacral agenesis, meningomyelocele with/without tethered cord), or acquired causes (tumor, trauma) [24]. The urological management is critical to quality of life in these children and should have the purpose of (a) preventing upper urinary tract deterioration, (b) decreasing the incidence and morbidity of urinary tract infections (UTIs), (c) achieving continence at the appropriate age, and (d) providing adequate sexual function. The management of the primary neuropathology must be accompanied by aggressive management of urological dysfunction, as these issues can cause major morbidity and significantly reduce quality of life.

Follow-up of these patients is aimed at assessing progress in the four areas mentioned previously. Patients doing well in these areas require little more than annual office evaluations and renal/bladder sonography. On the other hand, patients struggling with one or more of these areas need more medical attention. In order to assess a patient's progress along these lines, the potential urological complications of the disease, as well as their therapies, must be understood.

48.2
Potential Urological Complications

48.2.1
Urinary Tract Infection

Urinary infection is one of the most feared complications of neurogenic bladder dysfunction. Indeed, among the most common findings in these children is bacteriuria. In a study of 14 children with a normal upper urinary tract and no reflux, over a period of total 323 weeks, 70% (172 of 244) of the urine cultures that were obtained by clean intermittent catheterization were found to be positive ($\geq 10^4$ cfu/ml); of these, 152 (88%) grew common urinary tract pathogens, but 20 (12%) grew commensual microorganisms. It was found that regardless of the bacteria species, pyuria accompanies bacteriuria two-thirds of the time. However, only five symptomatic UTIs were observed [59]; therefore, it is critical to distinguish between symptomatic and asymptomatic bacteriuria. Other authors have also emphasized this. In their study, which evaluates the outcome of 38 babies with myelodysplasia managed with clean intermittent catheterization, Joseph et al. reported a bacteriuria rate of 42% (16 babies), but only 5% (2 babies) had symptomatic urinary infections and no infant required hospitalization because of urinary tract infections [29]. In a study of patients who had undergone ileocystoplasty, over 5 years of follow-up, only 20% of patients had had a symptomatic infection [33]. Likewise, after gastrocystoplasty, positive cultures were seen in up to 69% of patients, but symptomatic infections occurred only in 21–27% of patients

[15, 34]. It is important to note that there are no data demonstrating that treatment of asymptomatic bacteriuria is in any way beneficial, and it is well accepted that increased antibiotic use leads to more resistant microbes in the future.

48.2.2
Follow-up Implications

These findings suggest that routine urinalysis and/or urine cultures are not needed in asymptomatic patients with neurogenic bladder dysfunction. This concept is hard to impress on the primary care physician but is clearly supported by the data. The findings of urinalysis and culture should not result in any alteration in care. In addition to the risk of developing resistant organisms in that particular patient, the societal implications are clear. These tests are expensive and treatment of the results, when there are not demonstrable health benefits, is even more expensive. Furthermore, the general alterations in microbial resistance as a result of excessive antibiotic usage are significant, both in terms of risk and cost.

It is our belief that symptomatic infections in patients with neurogenic bladder dysfunction are not the result of particularly virulent bacteria. Instead, they are most often caused by an inadequate bladder management regimen. Most commonly, the cause may be traced to insufficient frequency of bladder emptying (we recommend every 3 h during the day) or incomplete emptying (many children, in their rush to spend as little time in the bathroom as possible, fail to completely drain their bladders). Both of these habits dramatically increase the likelihood of UTIs; hence, again, the emphasis during follow-up should not be on urine testing, but rather on education and monitoring of bladder-emptying practices. High intravesical pressures may also be a cause of UTIs and, in children with symptomatic UTIs, an effort should be made to make certain that intravesical pressures remain low.

48.3
Vescioureteral Reflux

Vesicoureteral reflux (VUR) is well known to be associated with pyelonephritis, hydronephrosis, and renal scarring. On the other hand, in otherwise normal children, it may have a benign natural history and many children outgrow the problem over time. In contrast, in children with neurogenic bladder dysfunction, it is a particularly ominous sign and heralds the onset of significant upper urinary tract deterioration. Indeed, in one study, two-thirds of the patients with vesicoureteral reflux secondary to neurogenic bladder dysfunction were reported to have upper tract deterioration [25]. In most cases reflux should be considered a warning sign of improper bladder management.

The incidence of VUR at birth in patients with myelodysplasia is low, reportedly to range between 0 and 24%, but it can increase rapidly to 60% in untreated or improperly treated patients [25, 38, 41, 45]. In contrast to patients who do not have neurogenic bladder dysfunction, once present, reflux cannot be followed using only antibiotic prophylaxis, as at least 50% of patients suffer upper tract deterioration.

This is likely because of the different pathophysiology of reflux in children with neurogenic bladder dysfunction. In non-neurogenic children, VUR is thought to be the result primarily of an embryological abnormality of the ureteral bud that results in an anatomical problem at the ureterovesical junction. This may be accentuated by voiding dysfunction. In contrast, most children with neurogenic bladder dysfunction are born with normal anatomy of the ureterovesical junction. In their cases, vesicoureteral reflux is most likely caused by high bladder pressures and resultant alterations in the trigonal musculature that distort the anatomy of the ureterovesical junction or are sufficient to force urine back through a relatively normal ureterovesical junction. It follows that management and follow-up should be directed primarily to restoring low bladder pressures, with antireflux surgery being used only as a secondary modality.

48.3.1
Follow-up Implications

The detection of VUR requires radiographic testing, which involves catheterization and exposure to ionizing radiation. Nonetheless the importance of the condition mandates testing for this condition. We believe that the initial testing for VUR should be done in the newborn period, either with a standard VCUG or, even better, as part of a flurourodynamic study. In the absence of reflux (in a patient who is doing well clinically), we do not recommend further VCUGs. On the other hand, the finding of reflux mandates aggressive urological intervention and follow-up. Although there is some controversy regarding the timing of instituting a treatment program in these children, we believe that the finding of an abnormality on these tests is an early warning sign of future problems. Even in the absence of newborn reflux, McGuire et al. documented the high rate of renal deterioration in untreated patients who had a leak-point pressure greater than 40 cm H_20 [42]. In contrast, we reported that in 35 neonates with myelomeningocele treated proactively with clean intermittent catheterization combined with anticholinergic medications, only two required vesicostomy (one due to difficulty in catheterization and one due to anticholinergic side effects) during the follow-up period ranging from 6 to 72 months. We saw no upper tract deterioration in that series [3]. Similarly, Edelstein et al. reported that only 15% of patients treated with early bladder management had upper tract deterioration, whereas 80% of the patients managed with observation had deterioration [17]. In another of our reports of patients who had treatment instituted during infancy, Wu et al. reported that only 13% of patients had upper tract deterioration [69]. Furthermore, we also reported that patients in whom treatment began as neonates had a decreased need for an artificial sphincter, as well as better bladder compliance and a lower augmentation rate after 5 years of follow-up [69].

Consequently, we believe strongly in proactive treatment; however, even if patients are not treated proactively, when either the VCUG or the flurourodynamic study demonstrate VUR or high intravesical pressures (in order to have high intravesical pressures, the leak-point pressure must be >40 cm H_20), immediate institution of anticholinergic medications and clean intermittent catheterization is recommended. Follow-up in these cases is frequent, with repeat urodynamic study within several months to document the reduction in intravesical pressure. In the absence of reflux, but with high pressures demonstrated, it has been our policy to recommend the institution of anticholinergic medication and intermittent catheterization, but this policy is not universal. If untreated, these children should undergo frequent urine testing and renal sonography at least every 3 months. The onset of UTIs or hydronephrosis would mandate some form of intervention. In those children with no reflux and low bladder pressures, treatment is more optional, but renal ultrasound at least every 3 months during infancy is recommended for follow-up.

In older children, follow-up studies are generally performed annually. This includes routine office evaluation and renal ultrasound. Other testing is predicated on three factors: UTIs; hydronephrosis; and continence. In the presence of UTIs or hydronephrosis, flurourodynamic studies are warranted. They will very likely demonstrate high intravesical pressures. An aggressive plan that lowers intravesical pressures and includes regular emptying with intermittent catheterization is warranted. Patient/family education is critical with intensive monitoring of the medication and catheterization schedule. This should reverse hydronephrosis and may reverse reflux.

Surgical treatment of VUR should be thought of as a second-line approach after optimal bladder management. In many cases control of abnormal bladder function will help reflux resolve spontaneously, or if not, at least it will prevent symptomatic infections. In addition, when surgery is necessary, the success rate is improved dramatically when bladder pressures are lowered [47]. Historically, this surgery had a high risk of failure, but in retrospect this was due primarily to inadequate bladder management post-operatively. With aggressive bladder management, the risk from anti-reflux surgery should be no higher than after traditional anti-reflux surgery. Some have even reported using endoscopic treatment for this type of reflux, although most surgeons prefer the safest, most reliable procedure possible. In any event, follow-up after antireflux surgery in this group is generally by ultrasound and VCUG. A good alternative to VCUG is a fluorourodynamic study to monitor bladder function. In follow-up, management of bladder dysfunction should be the highest priority.

48.4
Continence

Treatment of urinary continence is an important aspect of the management of patients with neurogenic bladder dysfunction. In infants this is obviously not a significant issue, as they are in diapers in any event. On the other hand, in older children incontinence causes major problems in daily social life and reduces the quality of life. We investigated self-concept in 50 patients with spina bifida. While no difference was found between continent patients with spina bifida (10 children) and controls, incontinent patients (40 children) had lower scores in social acceptance and global self-concept than controls [48]. The basic etiological causes of incontinence are high bladder pressures (either related to reflex contractions and/or poor compliance) or low outlet resistance (open bladder neck and/or poor urethral closure pressures). Historically, urinary diversion, indwelling catheters, and external collection devices were used for the treatment of incontinence [5, 12, 23, 37]; however, understanding the pathophysiology better allows for many treatment modalities that have obviated the need for urinary diversion in most cases; these include lowering bladder pressures (usually with medications and intermittent catheterization), and when needed, increasing outlet resistance (usually with some form of operative intervention). Furthermore, lowering bladder pressures to normal not only improves continence, but has the additional benefit of improving the upper urinary tract.

48.4.1
Follow-up Implications

Follow-up in these patients requires documentation of their continence status. This seemingly simple task is not as easy as might be expected. Patients have a natural tendency to tell their care providers what they think their providers would like to hear; hence, not infrequently, a patient will report that they are continent, yet on examination they are wearing diapers as opposed to underwear. On further questioning in an extremely non-threatening way, it often turns out that the patient is not as continent as they initially claimed.

Follow-up should again focus on bladder function. Primarily this requires investigation of the patient's regimen of medications and catheterization program. This is done by careful history taking, but is supported greatly by a catheterization diary showing the timing and volume of bladder catheterization, with the addition of documentation of the use of medications, as well as incontinence and fecal problems. When this is inaccurate or difficult to obtain, the next step is fluorourodynamic studies, in order to get more objective information on the cause of the incontinence.

In cases in which the outlet resistance is too low, an artificial sphincter or sling procedure may be used. These procedures require very careful follow-up as a number of patients have returned with new found hydronephrosis several years later [58]. In these instances, increasing the outlet resistance has led to an alteration in bladder function such that the bladder pressures are increased (and in some cases, unresponsive to anticholinergic medications). Careful urodynamic follow-up is critical.

48.5
Fecal Incontinence

Bowel problems are common in children with neurogenic bladder dysfunction. In infancy constipation is often seen and should be treated; hence, it is important to ask about this during routine follow-up and to treat it as necessary. The problems are different for older children. Once continence is important, most older children will be treated with some type of bowel regimen. Generally, the goal is to keep these children constipated, as this helps prevent fecal soiling; however, similar to urinary tract management, regular fecal emptying is critical. The plan must be individualized, but this can be accomplished via digital stimulation, suppositories, or even regular enemas [18, 56, 67, 68].

48.5.1
Follow-up Implications

Although not strictly in the urological realm, it is important to help manage the bowel program, as many of these patients will have fecal incontinence and require diapers for this reason alone, thereby defeating the purpose of treating urinary incontinence. In follow-up, bowel function should be monitored by history and bowel diary. Patient and family education in this area is very important. When independence becomes more of an issue, many families have found excellent benefit in the antegrade continent enema (ACE) procedure [22, 27]. This involves the surgical creation of an appendicocecostomy. The patients then do antegrade bowel flushes on a daily basis (usually tap water with soap suds each evening). This combined with natural constipation leads to excellent fecal continence in most cases. The procedure can be performed simultaneously with other reconstructive surgery.

48.6
Sexual Dysfunction

Sexual dysfunction in patients with neurogenic bladder dysfunction is under-appreciated and not well studied. Although these problems are not an issue during childhood, virtually all parents have "hidden" concerns about this and an open discussion of potential problems and therapies is universally welcomed. Virtually all patients will be affected as adults. The impact of the neurogenic lesion on sexual function is of course very different in male and female patients, so they should be assessed differently [6, 10]; hence, follow-up of these patients varies greatly by gender.

In females, menarche tends to come early [20]. The reasons for this are unclear but may relate to abnormalities of the central nervous system, perhaps due to the Arnold-Chiari malformation seen in many patients. Patients and their families should be made aware of this to reduce anxiety when it occurs, but few require treatment to postpone menarche. From a sexual-function standpoint, many of these patients have reduced sensation in the perineum; however, most have normal interest in sexual activity. The neurological deficit does, however, affect the ability to achieve orgasm. Although close to 100% of healthy controls can have orgasms, only 52% of women with neurogenic lesions (59% for the women with upper neuron lesions and 17% of those with lower motor neuron lesions) report orgasms [62–64].

These patients should have normal fertility and appropriate counseling should emphasize this; hence, it is very valuable to provide education on preventing unwanted pregnancies. In addition, these patients should be treated as "higher-risk" patients during pregnancy. They may have difficulty with intermittent catheterization, a high rate of UTIs during pregnancy, and although normal pregnancies have been reported, a number of patients will deliver early [28]. Furthermore, a relatively weak pelvic floor likely leads to a higher rate of uterine prolapse. In addition, these patients are at significant risk for a high rate of stress incontinence postpartum, related to pressure on an already weak pelvic floor. Many obstetricians recommend a caesarian section vs vaginal delivery to prevent further damage to the pelvic floor.

Sexual dysfunction of males can be divided into two separate areas, erectile function and fertility. The localization of the lesion (upper vs lower motor neuron) is important for its effect on the erectile response of the men. Erections require intact neurological function and can be attained both via S2–S4 (parasympathetic "reflex" erections) and T10–T12 (sympathetic "psychogenic" erections) [7, 39, 63]. Depending on the etiology of the neurological lesion, many men are affected. For example, loss of erection in the patients after spinal cord injury has been reported to be around 75% [11, 65]. Men with upper motor lesions have more frequent erections (92% had reflex erections in the study by Comarr et al. [13]) than men with lower motor neuron lesions, although in most cases they tend to be short in duration and insufficient for vaginal intercourse [11, 13]. Most patients with spina bifida have mixed neurological lesions and erectile function may be even less predictable.

Follow-up of erectile function in these patients requires a concerned, non-threatening discussion. When patients are ready, they should be offered treatment options as appropriate. Many will respond to oral agents, and if so, this is optimal. Sildenafil has been found to be safe and effective with success rates of 90–93% [21, 51, 60]. In patients with neurological erectile dysfunction, another popular treatment is the intracorporal injection of vasoactive agents. Usually a mixture phenoxybenzamine, phentolamine, and papaverine is used or, alternatively, prostaglandin E1 as a single agent [8, 9, 40]. Dosing must be monitored carefully as neurologically impaired patients are extremely sensitive to these medications and require relatively small doses. The complications of this method include priapism (especially with too large a dose), penile fibrosis, scarring, and dysesthesias [35, 39]. Many patients prefer other methods, but the lack of sensation in most neurogenic patients may make penile injections more acceptable. Finally, the surgical placement of penile protheses has also been reported [30]. Although popular in some situations, skin breakdown, the need for intermittent catheterization, urinary colonization and the lack of sensation make for a high rate of problems with the prostheses in these patients [32, 57]. Indeed, although there is a high initial success rate, 25% of patients with spinal cord injury and a penile prosthesis will require removal of the device due to erosion and/or infection. Follow-up of erectile dysfunction in these patients requires regular attention and ongoing education.

Fertility depends on many factors, including ejaculation and sperm quality. Ejaculation is a very complex event with numerous systems being involved, and the neurological control of this is quite complicated; hence, it is not surprising that very few men with neurogenic bladder dysfunction ejaculate appropriately. Indeed, in one study, only 4% of men with upper motor neuron and 18% of men with lower motor neuron lesions reported normal ejaculation [6].

Poor sperm quality is also problem for men with neurogenic bladder dysfunction [11, 16]. The possible reported reasons for this situation are recurrent urinary tract infections, stasis of prostatic fluid, testicular hyperthermia, sperm antibodies, and long-term usage of medications [49, 50]. Fortunately, for these patients, some new therapies are available. Electroejaculation has been used to induce ejaculation in a way that allows sperm collection for assisted reproductive techniques [7, 49]. Another approach is to obtain sperm directly from the testis or epididymis and use this for intracytoplasmic sperm injection. Again, education about the various options is important in the follow-up of these patients into adulthood.

48.6.1
Follow-up Implications

Follow-up of these patients requires an open, non-judgmental discussion of the issues. In women, a discussion of sexual function and acknowledgement of the potential for full fertility is critical. In contrast, men tend to have more sexual and fertility problems. In most cases, patients should be made aware that treatment options are available. Appropriate counseling is very valuable.

48.7
Tethered Cord

Tethered cord is defined as an abnormal fixation of spinal cord in patients with spinal dysraphism. Lumbosacral lipoma, diastometomyelia, spinal dysraphism, and fibrous post-operative adhesions are the main causes of this syndrome [14]. Development of tethered cord after meningomyelocele repair is an important potential complication, and at minimum, 3–15% of the patients are reported to be affected [55, 61, 66]. Indeed, by MRI scan, virtually all patients are affected. The fixation of the cord, combined with the normal tendency of the spinal cord to move upwards within the spinal canal with growth, leads to stretching of the spinal cord longitudinally. This is thought to decrease blood flow and results in ischemic neural damage [70]. The clinical manifestations of the syndrome are alterations in bladder function, progressive scoliosis, foot deformity, and loss of sensation in lower extremities [1, 2, 4, 19, 43]. Specific urological manifestations are incontinence (due either to sphincteric denervation or high bladder pressures) or, in some cases (somewhat ironically), bladder flaccidity that obviates the need for anticholinergic medications [31, 53–55, 71]. In one of our early studies of 18 patients with tethered cord, we reported that 9 had flaccid, 5 had uninhibited, and 2 had mixed hypertonicity and reflex contractions, whereas only 2 of the patients were normal [26].

The outcome of untethering correlates with the timing of diagnosis. The untethering procedure, when performed within 6 months of the onset of symptomatology, is significantly better at reversing symptoms than when the procedure is performed later. Fone et al. observed an increase in compliance or an improvement in detrusor–sphincter dyssnergia in 30% of the patients and urinary symptoms decreased in 14% of cases [19]. Similarly, Kaplan et al. reported that early untethering of the cord resulted in 60% improvement in urodynamic parameters and the percentage of increase in bladder volume was 12% [31].

48.7.1
Follow-up Implications

Follow-up in these patients requires a high index of suspicion for tethered cord. The development of tethered cord, either after closure of meningomyelocele or primarily in the patients with spinal dysraphism, takes a long time and may extend over several years. Yet early diagnosis is critical and often the urological symptoms occur before neurological deterioration [14]. In children who have undergone meningomyelocele repair, careful periodic neurourological monitoring should be performed to detect problems early and to thereby limit any morbidity of the tethered cord syndrome. Any change in urological symptoms should be investigated with the possibility of tethered cord kept in mind.

48.8
Bladder Augmentation

Often the therapy itself has side effects that require follow-up. One of the main examples of this relates to bladder augmentation. This procedure is commonly used in patients unresponsive to anticholinergic therapy, in order to lower bladder pressures and to create a larger reservoir for urine storage. Although life-saving in some cases and critical for continence in others, it carries its own risks. Follow-up depends on the bowel segment used. In most cases this is small bowel, generally ileum. Patients with an ileal augmentation are prone to hyperchloremic acidosis, mucous production, reservoir stones, perforations, and possibly delayed development of cancer [36, 46]. Patients who have undergone gastric bladder augmentation are more prone to hypochloremic alkalosis and hematuria/dysuria syndrome. There has been concern that chronic electrolyte abnormalities due to augmentation cystoplasty might lead to bone demineralization or growth failure, but this has not been demonstrated [44].

48.8.1
Follow-up Implications

Follow-up evaluations should focus on the potential problems. For example, a history of infrequent catheterization suggests an increased risk of perforation in patients who have had a bladder augmentation, and it is critical that patients be aware of this. In patients with reduced renal function, it is important to measure electrolytes regularly, and alkalinization should be used liberally when acidosis is present. Annual ultrasounds of the kidneys should look for both renal deterioration and reservoir calculi. The potential risk of developing neoplasia is also a concern. There is no consensus on the need for regular cystoscopy in patients many years after an augmentation; however, a high index of suspicion for possible malignancy is needed. Patients who have undergone gastric augmentations have less mucous and perforations, but can have hematuria and dysuria if they are incontinent or when they attempt to void on their own. They also can be prone to hypochloremic alkalosis. A high salt intake and periodic electrolyte measurements are appropriate. Again, as more experience is gained, periodic cystoscopy may be beneficial.

48.9
Self-Esteem

Too little attention over the years has been paid to self-image and quality-of-life issues in children with neurogenic bladder. There is, however, an increasing appreciation of their importance. Patients and families dealing with neurogenic bladder dysfunction not only have the usual issues in raising children, but have the additional burden of managing a chronic illness that requires frequent medical attention. In addition, many children have to deal with readily apparent disabilities, e.g., braces for ambulation or the use of a wheelchair. All these factors can play major roles in disturbing a child's self-image and reducing their quality of life.

48.9.1
Follow-up Implications

Follow-up in these patients should include regular psychological evaluation and counseling. The burden of illness in these families is considerable and can lead to significant family strife. This, in addition to the child's own disability, can cause significant psychological problems. Although medical care tends to focus on specific medical problems, periodic measurement of self-concept and quality of life would be very beneficial [48, 52].

48.10
Conclusion

Children with neurogenic bladder dysfunction can have a multitude of urological problems. These problems can be divided into four main categories, and therapy as well as follow-up should address them. These categories are as follows: (a) preservation of the upper urinary tract; (b) prevention of UTIs and reduction of their morbidity; (c) achieving continence at the appropriate age; and (d) providing adequate sexual function. Furthermore, taking all of the above into account, overall quality of life should be preserved.

Urological follow-up should address these points. In general, these patients should have an annual history (emphasizing potential problems and requesting information on problems that might be too embarrassing for the patient to bring up on their own) and physical examination (looking especially for signs of tethered cord). A catheterization/voiding diary is very helpful in obtaining further objective information on urinary tract function. In addition, to look for subtle signs of urinary tract deterioration, we recommend an annual renal/bladder ultrasound. Specialized testing is done only on an as-needed basis. In particular, urodynamic studies are recommended only when there is a problem with urinary tract infections, hydronephrosis, or continence, or when there is a question of a tethered cord. For all patients, attention to psychological aspects, especially quality of life, is important.

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Follow-up in Adults with Neurogenic Bladder Dysfunction

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49.1
Introduction

Voiding disorders in neuropathic patients encompass a large group of diseases that can be attributed to neurological, anatomical or functional causes.

Most cases of neuropathic bladder are caused by myelomeningocele with or without tethered cord. Children born with myelomeningocele face the morbidity of urinary tract complications after they have survived the neurological complications of the first years of life [6]. Neurophatic bladder dysfunction is also found in children with anorectal agenesis when the neuropathy is usually due to associated spinal anomalies. Occult spinal dysraphism can also cause a neurophatic bladder. In the majority of the spina bifida cases, the lumbosacral region is involved, leading to neurogenic disturbance of urogenital, colorectal and pelvic floor function. Further causes of neurophatic bladder are acquired spinal cord lesions including trauma and neoplasms.

Historically, bladder management consisted primarily of reflex voiding or chronic clean indwelling catheterization (CIC), and complications (such as infections, hydronephrosis, vesico-ureteral reflux and renal scarring) were common in many children.

In the past years, better knowledge of the evolution and prognosis of neurological bladder has enabled the development of pertinent follow-up strategies and the screening of risky situations. This approach resulted in increased life expectancy for patients suffering from neurogenic bladder; thus, abnormalities of bladder behaviour caused by neurogenic dysfunction in childhood presently represent a common finding in adult life.

49.2
Neuro-Urological Dysfunction

Bladder dysfunctions can be divided into two basic categories: first, bladder failing to empty successfully and, second, those failing to store urine adequately. Failure to store and empty in combination also occur [10].

In 50% of patients with neurogenic dysfunction, as myelodysplasia, the detrusor has a normal pattern or a low pressure, while in the remaining cases elevated intravesical pressures and or elevated leak-point pressure can be present and deteriorate upper urinary tract [46].

One of the most important aspects of the urological care for patients with neurovescical dysfunctions is the periodic re-evaluation. Neuro-urological assessment is never definitive [8].

A normal lower urinary tract function in the early years of life of patients with neurogenic dysfunction is not a guarantee for the absence of future problems. The bladder undergoes changes at puberty that alter storage and voiding function [50]. These patients needs a strict follow-up into adult age because they are at risk for development of tethered cord syndrome, caused by a traction on the lumbar spinal cord between two fixation points [17].

There is a clinical impression that bladder function deteriorates at puberty especially in males. A change in bladder behaviour usually indicates a change in the neurological status and is an absolute indication for a neuro-urological evaluation [17]. A number of patients do not demonstrate any changes until puberty when accelerated growth put increased tension on the neural elements. Oftentimes, these changes may be stabilized or reversed with a second look laminectomy to remove scar tissue that may have formed as a results of the closure and tethering of the cord or nerve roots, or both; therefore, in children with identifiable bladder disease the general tendency is to worsen as ageing produces muscle and nerve degeneration in the bladder wall [22].

The most worrisome change in bladder behaviour is the development of increased bladder outlet resistance [44], presumably from growth of the prostate in males and estrogenization of the urethra in females [33]. Both conditions, which carry more danger than advantage, increase leak-point pressure, can alter voiding function and cause ureteral obstruction. In presence of poor compliance, elevated intravesical pressures and bladder wall thickening may subsequently have renal failure. Renal failure can also be accelerated by vesico-ureteral reflux [37].

At long-term follow-up the neurogenic bladder of children appears to behave in a manner remarkably similar to that seen in bladder outflow obstruction in later life [31]. In cases of bladder dysfunction related to outflow obstruction 60% of patients have high pressures and 40% have chronic retention of urine with overflow.

The timing and frequency of any change in the external urethral sphincter are important in planning future surveillance and treatment of these children. Early detection of abnormalities is of major importance since it may alter the incidence of future urinary tract deterioration and the chances for continence [24, 25].

At all ages, renal failure is the commonest cause of death. In children, the risk of renal failure is strongly related to the sensory level of the spine. Renal failure is rare with sensory levels at or below L4, and common at or above T10 [16]. Renal failure has been reported as a commonest cause of death in adult patients with spina bifida [42]; however, renal failure can occur even with apparently minor neural tube defects such as occult spinal dysraphism. In patients with a neurophatic bladder secondary to occult spinal dysraphism, the incidence of renal failure was 14.5% at 6–18 years of follow-up, despite adequate management of the bladder [41]. When urine is stored in intestinal reservoirs, the incidence of renal deterioration is about 20% at 10 years of follow-up [11]. In those who have reached adulthood, life expectancy is still shortened. At least 10% of patients were known to have died before their expected time [42].

The change in the neurological function can also occur early in childhood [37]. As the child grows, there is a natural tendency for the physical anomalies to deteriorate. The spinal deformity becomes more pronounced. The loss of mobility encourages obesity which, combined with the collapsed spine, makes much of the lower half of the body invisible to the patients.

The management of the primary neuro-pathology must be accompanied by aggressive management of urological dysfunction, as it caused significant morbidity and altered significantly quality of life. It is desirable that urological management and follow-up be organized in childhood [51].

49.3
Risk Factors of Renal Failure

The leak-point pressure, i.e. the detrusor pressure at which incontinence occurs, represents the most significant risk factor for upper urinary tract damage. There are no other significant prognostic factors in upper urinary tract changes. The classical criteria of bladder disequilibrium (i.e. post-void residual urine, urinary infection, vesicoureteral reflux, uretero-hydronephrosis, lithiasis and incontinence) reflect the deterioration when it occurs, but they do not have a good prognostic value.

The primary goal in the management of patients with neurogenic bladder dysfunction is preservation of kidney function. To achieve this goal, the bladder should function as a low-pressure reservoir. Obstructive uropathy and high bladder pressures during a significant part of the filling phase are the most important causes of kidney failure in these patients.

Treatment has to be aimed at reducing the storage pressure to less than 40 cmH_2O and maintaining continence by CIC, antimuscarinic drugs, bladder augmentation and an implant of a artificial urinary sphincter, if necessary [47]; therefore, it should have the purpose of decreasing the risks of urinary tract infections, to maintain continence and to provide adequate sexual function; moreover, bladder management cannot be considered in isolation from bowel management. Patients with neurogenic bladder dysfunction can only stay clean by a process of controlled constipation.

49.4
Upper Urinary Tract Alterations

Normal micturition consist of a synergic action between the detrusor muscle of the bladder and the external urethral sphincter: five to eight times per day the external urethral sphincter relaxes, followed by a contraction of the detrusor muscle and expulsion of stored urine from the bladder. This synergy between the detrusor and the external urethral sphincter is controlled by a specific area, the pontine micturition centre.

Lesions in the pathway between this area and the spinal cord often result in elevated bladder pressures, decreased bladder compliance [19], detrusor–sphincter dyssynergia or areflexia with elevated post-void urine residual [2, 4, 48], all conditions causing upper urinary tract damage.

All hyperreflexia are not dangerous in the same way: they are more hazardous if the contractions are strong, prolonged and frequent; otherwise, they may just manifest as a brief peak of hyperpressure but much less harmful than hyperpressure of the filling phase.

Detrusor–sphincter dyssynergia is a condition in which an involuntary contraction of the detrusor is accompanied by an involuntary contraction of the external urethral sphincter and, consequently, urine is not expelled without force from the bladder. In this situation the electromyographic activity fails to became quiescent during either a detrusor contraction or a sustained increase in intravescical pressure. This condition results in a low-compliant and thick-walled bladder, elevated retrograde pressure in the ureter and in the renal pelvis, hydronephrosis, and even renal scarring and terminal renal failure [13]. The upper urinary tract alterations are initially reversible by continuous catheterization or by restoring detrusor pressure to an acceptable level, whereas the renal function will deteriorate rapidly if the duration of exposure to high pressure is prolonged.

The leak-point pressure has a main role in the risk for urinary tract deterioration and, if the pressure is below 40 cmH_2O, upper urinary tract is unlikely [27]. When bladder leak-point pressure is ≤40 cmH_2O, there is no vesicoureteral reflux and only 10% of dilatation on intravenous pyelography (IVP) is detected. When leak-point pressure is >40 cmH_2O, 60% of reflux and 80% of upper urinary tract deterioration is found [26].

The high and sustained intravesical pressure (>40 cmH_2O), in presence of an elevated leak-point pressure (>40 cmH_2O), can obstruct the delivery of the urine bolus from the renal pelvis to the bladder. Detrusor hyperpressures may cause bladder alterations, such as trabeculae and diverticula, and moreover may damage the watertightness of uretero-vesical junctions, inducing vesico-uretero-renal reflux and facilitating urinary infections.

Vesicoureteral reflux may result from detrusor hyperreflexia or detrusor–sphincter dyssynergia. In one report, urodynamic evaluation of 36 infants with myelodysplasia showed non-coordination of the detrusor and external urethral sphincter, synergic activity of the sphincter, and no sphincter activity in 18, 9, and 9 patients, respectively [2]. Infants with non-coordination of the detrusor-external sphincter were at high risk for urinary tract deterioration. Of that group, 13 of 18 (72%) developed hydro-ureteronephrosis, compared with two of nine (22%) with synergy and one of nine with no sphincter activity.

The main effects on upper urinary tract are represented by pyelonephritis, renal scarring and hydronephrosis, both expressions of vesico-ureteral reflux or obstruction caused by elevated bladder pressures [7, 21].

The prognostic value of leak-point pressure is demonstrated by the survival curves testing the rate of upper urinary tract degradation according to its dilatation and the leak-point pressure: a patient with a leak-point pressure exceeding 40 cmH_2O has seven times more risk of upper urinary tract damage than someone with stable leak-point pressure [3].

Children with synergic sphincter activity rarely deteriorate. Only those who convert to a dyssynergic pattern during follow-up do so and usually within a year from the conversion. Similarly, children with complete denervation of the sphincter were unlikely to show signs of urinary tract deterioration. Seldom is this condition present in children with increased outlet resistance from extensive denervation fibrosis of the striated muscle component of the sphincter.

49.5
Urinary Tract Infections

Urinary tract infections (UTIs) represent one of the most frequent and feared complications in patients with neurogenic bladder dysfunctions and commonly represent the reason for urological consultation. In adults they can present as bacteriuria (>100,000 cfu/ml), the most common finding, or as bacteriuria associated with irritative symptoms, haematuria, fever, shivering and smelly urine. Sometimes they appear in subtle features as intense renal and bladder pain, urinary leakage, or micturition changes, lethargy or general malaise and discomfort.

In the long term, UTIs are more frequent in the patient groups with continuous bladder drainage, whereas the intermittent catheterization seems to be the safest method for neurogenic bladder patients in terms of urological long-term complications. Pyelonephritis and epididymitis are main causes of infectious complications.

The main risk factors for UTIs associated with neurogenic bladder dysfunction are: impaired voiding; overdistention of the bladder; elevated intravesical pressure; post-void residual urine volume; vesico-ureteral reflux; urinary tract obstruction; instrumentation; and increased incidence of stone formation; also, decreased immunity, pregnancy, repeated urethral trauma, anatomical anomalies, perineum hygiene, presence of indwelling or suprapubic catheter. The suprapubic catheter is moreover frequently complicated by a high frequency of bladder lithiasis.

Prolonged or recurrent infections in the lower urinary tract is also one of the factors interfering with antireflux mechanism causing reflux of infected urine to the kidney. This situation may lead to stone formation in the kidney and to the development of progressive failure of the affected kidney.

Symptomatic infections in patients with neurogenic bladder dysfunction are frequently determined by an incomplete emptying of the bladder or by an insufficient frequency of voiding.

The CIC is the preferred method of adequate bladder drainage, with a significant low rate of complications compared with indwelling urethral catheterization [12].

49.6
Incontinence

Incontinence represents a feared complication of neurogenic bladder dysfunction patients, occurring when elevated bladder pressures overcome urethral resistance. An unsolved problem of urinary continence may have a serious impact on quality of life (QoL); however, most of these patients live with their handicap for their whole life and often adapt to it in a remarkable way.

Although incontinence is not always a barrier to a fulfilled life, those who are continent have a better view of self-worth. In girls, social acceptance and views of overall self-worth, and in boys, scholastic competence, social acceptance, physical appearance and behaviour, are all improved by continence [28].

Incontinence should categorized as primary or secondary, continuous dribbling or occasional leakage, associated with stress or urge and nocturnal or diurnal.

Incontinence in neurogenic bladder dysfunction is multifactorial and often related to detrusor hyperreflexia, decrease compliance and sphincteric or pelvic floor incompetence. The leak-point pressure in these cases is generally low.

Documentation of the bladder status can be achieved with careful history taking, by a micturition and catheterization diary and documentation of the use of medications, as a urodynamic evaluation. Time and volume of bladder catheterization, and finding of associated faecal incontinence, allow a complete evaluation of the causes related to urinary incontinence.

Hyperreflexia and decreased compliance can be addressed by medical or surgical treatment and eventually in combination with CIC. In presence of lower urethral sphincter resistance, a sling procedure or an artificial sphincter can be used, but surveillance is critical, because with ageing, many patients become obstructed and can develop hydronephrosis years later.

49.7
Sexuality and Fertility

Sexual function is not adequately evaluated in this group of patients. Lack of privacy and dependence on others for normal daily living do not allow normal sexuality. Moreover, they have low social and sexual confidence. As patients with neurogenic bladder dysfunction now have increased life expectancy, this is recognized as an important QoL issue [29, 30].

Sexual dysfunction impacts differently between males and females and is dependent on neurological level of the lesion [5]. Theoretically, the effects on penile erection, vaginal lubrification and orgasm are related to the level and completeness of the lesion.

In females reporting reduced sensations in perineum, they refer normal interest in sexual activity but difficulty in achieving orgasm; therefore, they have a normal fertility. Moreover, they are considered at high risk of upper urinary tract damage during pregnancy, due to the high rate of UTIs and difficulties with intermittent catheterization. These conditions can also cause early delivery [15].

In a series of 20 pregnancies in spina bifida patients, 35% were delivered before 37 weeks [38]. Vaginal delivery is possible, although complications related to deformity of the pelvis frequently occurs [36]. High rate of uterine prolapsed and stress incontinence can be detected post-partum, both related to the weakness of the pelvic floor.

In males, sexual dysfunction is divided into impotence and infertility. Erections and ejaculation are largely under neurological control [14]. Erections are claimed by about 80% of adolescent males, although most of the erections are probably reflex in nature and not in response to sexual stimuli [9, 40].

Men with upper motor neuron lesions have more frequent erection than lower motor neuron lesions, and many of them respond to medical therapy with oral agents or intracorporeal injection of vasoactive agents [23, 39]. Sildenafil may be used with appropriate dose reduction. In the only trial to date, 80% of men responded to a dose of 50 mg [29, 30]. Penile prosthesis are not popular for the high rate of infections and erosion among these patients.

Fertility is related to ejaculation and sperm quality. The ejaculation is compromised in patients with neurogenic bladder dysfunction and also sperm quality is impaired by recurrent UTIs, testicular hyperthermia and stasis of prostatic fluids and long-term use of medications [35]. Follow-up in these patients requires counselling on these issues, in particular among women, to let them know the potential for fertility. In contrast, men tend to have more sexual problems and counselling is focused on the different treatment options available.

49.8
Follow-up in Adults

The primary goal in the management of neurogenic bladder dysfunction is the preservation of the kidney function. Secondary end points are to maintain continence, decrease the risk of UTIs and allow adequate sexual function, if desired [1].

Initial clinical assessment in all patients with neurogenic bladder dysfunction consists of urinalysis, urinary culture, urinary ultrasonography (US), nuclear scanning, frequency–volume chart (FVC), plain abdominal X-ray, cystourethrography (CUG), urodynamic evaluation (UDS) and cystoscopy [32].

Invasive tests requiring urethral catheterization can be easily performed, because the majority of the children are already on the CIC regimen. The FVC, CUG, UDS and cystoscopy will reveal the aetiologies of urinary incontinence and will suggest the appropriate management that will improve patient's QoL.

Cystoscopy is an essential part of the initial evaluation of all patients with neurogenic bladder dysfunction, aiming to detect stones and neoplasm both causes of irritative symptoms and or haematuria.

In the initial phase, it will be interesting to have a starting intravenous pyelogram that may never be redone but which may serve as a subsequent reference document. If risk factors are not detected, patients are allowed to evacuate urine by abdominal straining or with intermittent CIC. Catheterization with a 8- to 12-F catheter is necessary three to six times a day, depending on urinary volume. Prophylactic antimicrobials and sterile procedures are not always necessary. In absence of changes in urinary status, follow-up assessment is repeated every 1–2 years with urinalysis, urine culture and renal and bladder US scan.

Asymptomatic patients with neurogenic bladder dysfunction do not need routine urinalysis. In the follow-up, more than just treating asymptomatic patients, leading to more resistant microbes, training patients on bladder emptying practice has a main role.

After obtaining information on the bladder conditions, if risk factors for deterioration of upper urinary tract are observed, monitoring should be more frequent.

In the case of low-pressure system, urinalysis and urine culture, post-void residual urine volume and renal US study are indicated every 1–2 years, if no change in clinical symptoms suggests modification of the bladder's pressure status.

Patients with elevated intravesical pressures or decreased compliance are monitored with a post-void residual urine volume, urinalysis and urine culture every 6 months and UDS evaluation every year, to exclude progression toward upper urinary tract deterioration.

If the external sphincter is synergic with high detrusor pressure during filling, a yearly renal US is sufficient to monitor the upper urinary tract.

Patients with outflow obstruction in the form of detrusor–sphincter dyssenergia with or without high detrusor pressure during filling are monitored with a post-void residual urine volume and urine culture every 3 months, US renal scan every 6 months and urodynamic evaluation every year, to exclude neurological progression.

In symptomatic patients, urinalysis has to be associated with renal and bladder scan to control bladder voiding or upper tract dilatation, which can maintain the infection. If the patients have recurrent UTIs or hydronephrosis is noted during follow-up, a voiding cystourethrogram is necessary to look for vesico-ureteral reflux.

Patients with vesicoureteral reflux should receive antibiotic prophylaxis, anticholinergic medication to lower detrusor filling and voiding pressures, and CIC to prevent urinary tract deterioration. The efficacy of this regimen was demonstrated in a sequential non-randomized study comparing prophylactic (CIC and anticholinergics) and expectant treatment in patients with these urodynamic findings. During 5 years of follow-up, the upper urinary tract deteriorated less often in the treated group (8 vs 48%) [18].

Intervention to prevent upper urinary tract deterioration is undertaken when there are signs of outflow obstruction or elevated detrusor pressure on filling, or both. High bladder filling and voiding pressure, especially when associated with uncoordinated external urethral sphincter, are signs suggesting that either bladder decompensates or upper urinary tract deterioration will occur.

If the patients become incontinent on intermittent catheterization despite a frequent emptying schedule, this may be due to elevated bladder filling pressure, uninhibited detrusor contractions, low urethral resistance or excessive urine volume.

Conservative treatment primarily comprises CIC with anticholinergic drugs, antimicrobials and eventually diapers [24, 25]. Appropriate therapy to treat elevated bladder filling pressure and or uninhibited detrusor contractions is necessary using anticholinergic drugs to lower detrusor tone and contractility. Urethral resistance can be raised with the use of alpha-sympathomimetic agents. Both therapies are necessary to improve continence between catheterizations.

There is strong evidence that starting CIC early in life improves the outcome of bladder function at least up to puberty. Comparing patients who started CIC at a mean time of 7 months vs a mean time of 45 months, all measured variables were better, with a hydronephrosis in 27 vs 58%. Moreover, the deterioration of renal function occurred earlier in the group whose CIC had been started late [20].

If urinary incontinence, detrusor overactivity and low bladder compliance and capacity are intractable with drug therapy, reconstructive surgery should be considered.

Augmentation cystoplasty is a surgical procedure in which a detubularized segment of intestine (i.e. ileum, colon, or stomach) is added to the bladder to increase capacity and lower pressure. The procedure usually results in the achievement of urinary continence. Augmentation cystoplasty is suitable for the patient with poor compliance or uninhibited detrusor contractions, not responding to medical therapy [34].

If the bladder has low compliance or cannot accommodate 120–160 ml of urine, then augmentation cystoplasty may be needed to keep the filling pressure low enough to allow the upper urinary tract to drain freely into the bladder and to maintain continence for an acceptable period of time. The need for CIC was once thought to be a complication of augmentation surgery, but this should be an expected outcome for patients with neurogenic bladder [43].

If drug therapy fails to raise urethral resistance sufficiently to maintain continence, surgery may be required to improve bladder neck resistance.

Urinary diversion is rarely performed presently in children with neurogenic bladder dysfunction [45]. Ileal conduit, a low-pressure system introduced at the beginning of the 1950s for the management of children with neurogenic bladder dysfunction, was considered the treatment of choice for reflux, hydronephrosis or urinary incontinence, but it resulted in many clinical problems. Recurrent episodes of pyelonephritis with resultant renal scarring, renal calculi, strictures of the ileum and stomal stenoses are common long-term complications.

49.9
Conclusion

The aim of follow-up in cases with neurogenic bladder dysfunctions is to evaluate bladder modifications in order to prevent upper urinary tract damage, reduce the incidence of UTIs and to preserve continence and adequate sexual function [49].

Patients should have a thorough examination and an individual plan for treatment and follow-up of their urinary tract dysfunction. Patients without problems in one or few of these areas require medical attention as an annual office evaluation and renal and bladder scan. Patients coping with one or more of these complications require medical attention to assess progress along these potential urological complications of the disease.

Certainly, the presentation of risk factors (i.e. elevated leak-point pressure) and urinary complications will lead to changes in follow-up and treatment plans.

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